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Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	40	6	7 or total of 15 images
Review Article	5000	250	80	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city

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All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

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References

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Journal Article: Stephane A. Management of Congenital Cholesteatoma with Otoendoscopic Surgery: Case Report. Turkiye Klinikleri J Med Sci 2010;30:803-7.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press;2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme;2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland;1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dçent Res. 1974. Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5):1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

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CONTENTS

ORIGINAL ARTICLE

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Rare Extrapulmonary Tuberculosis in Immunocompetent Adults: Experience of a Tertiary Hospital

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Abstract

Objective: Tuberculosis (TB) is an infection that can involve all tissues and organs. Although pulmonary TB (PTB) is more common, extrapulmonary TB (EPTB) is still a major clinical problem. The incidence of EPTB is 35.1% and in recent years; there has been an increase in EPTB case reporting in our country. In this study, we retrospectively investigated the clinical and laboratory characteristics of rare EPTB cases.

Methods: The study included rare EPTB patients diagnosed and/or followed up in our clinic. Cases with pleural TB and lymph node TB were excluded from the study. The diagnosis of EPTB was made by clinical, microbiological and/or histopathological and/or radiological findings and response to treatment. The demographic features, clinical findings and laboratory values were recorded from patient files, and were evaluated in terms of EPTB.

Results: Fifty patients were included in the study (mean age=34±15.8 years, female/male=33/17). The most frequently involved organ was peritoneum (n=13, 26%). There was multi-organ involvement in 4 cases (8%). Co-existence of EPTB with PTB was determined in 9 cases (18%). Four patients had a history of TB and 14 had a history of contact with TB. All the cases were human immunodeficiency virus-negative, and one case was hepatitis B surface antigen positive. The major complaints were abdominal pain, weight loss, night sweats, fever, and cough. Twenty-three patients had normal chest radiographs and the mean duration of treatment was 9 months.

Conclusion: TB is a serious public health problem in Turkey as well as all over the world. Since it is a treatable disease, early diagnosis and treatment have utmost importance for avoiding the serious complications of rare EPTB forms.

Keywords: Tuberculosis, extrapulmonary tuberculosis, adult tuberculosis

INTRODUCTION

Tuberculosis (TB) is a granulomatous infectious disease that can involve all tissues and organs of the body. Although it is a preventable and curable disease, it still exists as one of the major health problems in the world (1). In Turkey, the incidence of extrapulmonary TB (EPTB) has been reported as 30-45% (2-4). EPTB frequently involves lymph nodes and pleura, and less frequently includes bones, joints, genitourinary system, skin and soft tissues. In recent years, there has been an increase in the number of EPTB cases (1,3,5-7). One should consider EPTB in the differential diagnosis of almost every infection, particularly in countries where TB is endemic. The ratio of EPTB to pulmonary TB (PTB) changes according to geographical, social, ethnic, and economic parameters (8-10). EPTB develops as a result of lympho-hematogenous dissemination of the primary infection and subsequent latency of the disseminated TB bacilli, which then may acquire reactivation in case of reduced body resistance or increased susceptibility. The disease may occur in any stage of life and may involve any organ (4-11). The latency period in different organs ranges from 6 to 600 months (4). It is not yet clear why TB bacilli show reactivation in the lungs in some cases and in other organs in other cases (4,8). Female gender, history of contact with TB, smoking and end-stage renal disease have been implicated as factors affecting reactivation in organs (4,12). Studies on rare EPTB cases are limited (13-19). In this context, different clinical courses of TB render diagnostic difficulties in terms of different involved organs and rarity of EPTB. Difficulty

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in diagnosis results in delayed treatment, therapeutic problems, and increased costs as well as increased morbidity and mortality. The purpose of this study was to determine the demographic and clinical features of rare EPTB cases, to show that possible complications of EPTB can be prevented by early diagnosis and therapy, and to underline that EPTB should be considered among other disorders in differential diagnosis.

METHODS

Study Design, Setting and Population

We designed a retrospective study of EPTB cases diagnosed and/or followed up in a tertiary training hospital for chest diseases and thoracic surgery. The study was approved by the Local Ethics Committee of the Institution and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Since our study was retrospective, patient consent forms were not obtained. The data was authorized by the hospital's academic committee, provided that the patient's identity remained confidential. The study included EPTB cases followed up in our clinic. The criteria for exclusion were as follows: 1) Immunosuppression, 2) Presence of malignancy, 3) Pleural TB, 4) Lymph node TB, 5) Age under 18.

Data Source

The clinical and laboratory data of EPTB cases hospitalized in our clinic were obtained from patient files retrospectively.

Additional Covariate

The EPTB cases were evaluated in terms of age, gender, contact with TB, co-morbidities, concurrent PTB, history of contact with TB, tuberculin skin test (TST), radiological and bacteriological findings, diagnostic and therapeutic features and extrapulmonary organ involvement.

Definitions

There was at least one of the following diagnostic criteria in cases with definitive diagnosis of EPBT (20):

- Determination of the presence of acid-fast bacteria in the direct microscopic examination and/or culture of biopsy material obtained from extrapulmonary organs,

- Presence of necrotizing granulomatous inflammation in the biopsy material,

- Consistent with TB, TST positivity and response to anti-TB treatment,

- Clinical picture: Cough, expectoration, night sweats, weight loss, malaise, fever.

TST was accepted as positive when the induration diameter was ≥10 mm in patients without Bacillus Calmette-Guérin (BCG) scar, and ≥15 mm in patients with BCG scar (21).

Statistical Analysis

A descriptive analysis was performed to evaluate patient demographics and data.

RESULTS

The study included 50 cases with EPTB. Of the cases, 69% were female and the mean age was 34±15.8 years. Four cases (0.8%) had a history of TB and 16 (31%) had contact with TB. The demographic features of the cases are summarized in Table 1. All cases were human immunodeficiency virus negative and one case was hepatitis B surface antigen positive. Concurrent PTB was present in eight patients (16%). Three of eight cases had acid-fast bacilli-positive sputum and five of eight cases had positive culture for TB. Pulmonary radiology was normal in 23 patients. The mean duration of treatment was 9 months, including isoniazid, rifampicin, ethambutol, pyrazinamide (HREZ) regimen in the first 2 months and isoniasid, rifampicin (HR) regimen in the remaining 7 months. The most frequent symptoms were abdominal pain and weight loss followed by cough, fever, night sweats, expectoration, chest pain, and anorexia as expected in TB. The distribution of symptoms on admission is shown in Table 2. The diagnosis of EPTB was mostly histological. In 92% of our

Table 1. Demographic features of the extrapulmonary tuberculosis cases

	n (%)
Number of cases	50
Gender	
Female	33 (66)
Male	17 (34)
Mean age, years	34±15.8
History of smoking	
Smoker	36 (72)
Non-smoker	11 (22)
Ex-smoker	3 (6)
Tuberculin skin test*	24
Positive	14 (28)
Negative	10 (20)
Previous history of tuberculosis	4 (8)
History of contact with tuberculosis	14 (28)
Comorbidity	
Hypertension	4 (8)
Diabetes mellitus	1 (2)

*Tuberculin skin test was available in 24 cases. Rest of the data is missing

cases, EPTB was diagnosed histopathologically and in eight cases with concurrent PTB, smear/culture was also positive in addition to histopathological positivity. No culture was made from biopsy specimens. In our EPTB cases, gastrointestinal system was the most frequently involved system. The distribution of cases according to organ involvement is shown in Table 3.

DISCUSSION

EPTB causes diagnostic and therapeutic difficulties because it has different clinical courses in different organs. The consequences of this situation are delayed treatment and cost problems, as well as increased morbidity and mortality. In our study, most cases were female, there was a history of contact with TB in 28% of the cases, classical TB symptoms like weight loss, fever, night sweats were frequently present although the symptoms changed according to the involved organ, the most frequently involved system was the gastrointestinal system, and the most frequently used diagnostic method was histopathological examination. The incidence of EPTB has been reported to be 4.5-53% (2,3,5,9,22). This variable incidence of TB is related to geographical, social, ethnic, and economic parameters. The disease is more frequent in women than in men (4,6,9,10). Similarly, we had more female patients in our study. Although the role of gender in EPTB is not fully clarified, cellular immunity, hormonal changes and socio-economic and cultural status are thought to be related to this difference (12,23,24). EPTB is most common in the 30-58 age range (3,5,6,10,12). The mean age of our patients was consistent with this age range. Lin et al. (12) reported the prevalence rate of EPTB as 5.9% at ages ≤24 and as 54.9% at ages ≥60. This difference in prevalence may be related to changes in the immune system with aging. In their study on the association of smoking with TB, Kolappan et al. (25) reported that the rate of TB increased parallel to the number of cigarettes smoked and length of smoking period. On the other hand, EPTB is more frequent in non-smokers (4,26). Lin et al. (12) reported a negative correlation between smoking habit and EPTB. In our patient group, 72% were smokers, indicating a finding that might be related to high rate of smoking in Turkey.

An important clue in the diagnosis of EPTB is the history of patient's previous contact with TB. Musellim et al. (4) reported an EPTB rate of 76.6% within 5 years after contact with TB. According to another study, there was no significant difference between PTB and EPTB in terms of contact history with TB (8.9% vs. 8.4%, respectively) (9). Two patients with breast TB in our study were sisters with a family history of PTB (27). Cases of PTB under treatment and included in the screening program for TB in the family should also be carefully examined for the possible presence of EPTB.

Table 2. The symptoms of extrapulmonary tuberculosis patients referred to hospital

	n (%)*
Abdominal pain	17 (34%)
Weight loss	17 (34%)
Night sweats	14 (28%)
Cough	14 (28%)
Fever	12 (24%)
Expectoration	11 (22%)
Chest pain	9 (18%)
Anorexia	8 (16%)
Malaise	6 (12%)
Others**	7 (14%)

*There were cases with multiple complaints,
**Others include hoarseness, breast mass, testicular mass, tongue ulcer, knee pain, skin ulcer, diarrhea, menstrual irregularity

Table 3. Distribution of the extrapulmonary tuberculosis cases according to organ involvement

Extrapulmonary involvement	n	%
Peritoneum	13	26
Peritoneum + pleura	3	6
Intestines + lung	3	6
Tongue + lung	3	6
Peritoneum + lung	2	4
Intestines	2	4
Liver	2	4
Larynx + lung	2	4
Larynx	2	4
Breast	2	4
Endometrium	2	4
Peritoneum + spleen	1	2
Peritoneum + miliary	1	2
Lip + lung	1	2
Epiglottis + lung	1	2
Chest wall	1	2
Peritoneum + vertebra + lung	1	2
Pericardium	1	2
Knee joint	1	2
Skin	1	2
Parotid gland	1	2
Peritoneum + pericardium + pleura	1	2
Thyroid	1	2
Testis + vertebra + psoas abscess	1	2
Liver + spleen + lung + lymph node	1	2

Co-morbidities such as long-term corticosteroid use, Chronic Obstructive Pulmonary disease, alcoholism, diabetes mellitus, chronic renal failure, malignancies, and immunosuppression increase the development of TB (28). Lin et al. (12) found that the presence of co-morbidity is insignificant for the development of EPTB and PTB. On the other hand, Gonzalez et al. (29) reported hepatic cirrhosis as a risk factor for the development of EPTB. In our patient group, there was only one case with diabetes mellitus. The symptoms and findings in EPTB vary according to the involved organ and concurrent PTB. In our patient group, the most common symptoms were cough, expectoration, weight loss, night sweats, and anorexia accompanied by organ-specific symptoms in most cases, consistent with data from relevant studies (3,6,9,12). The diversity of systemic or pulmonary symptoms leads patients to admit doctors in various medical branches, resulting in diagnostic difficulties and delayed treatment unless TB is suspected. Demiralay (9) reported that the time between the onset of symptoms and establishment of EPTB diagnosis was 154±39.2 days. The diagnosis time in EPTB is shortest in pleural TB and longest in skeletal system TB (9,29). This finding may be related to a higher incidence of pleural TB, which is suspected and therefore diagnosed earlier. *Mycobacterium* TB culture is the gold standard in the diagnosis of TB (1). The diagnosis of EPTB is more difficult than the diagnosis of PTB. Histopathological examination and culture of biopsy material are important for the diagnosis of EPTB (5,8). In our patient group, no culture was made from biopsy specimens, and this was related to the fact that EPTB was not considered in differential diagnosis in the preoperative period. The clinical suspicion of EPTB is an important step in diagnosis, leading to establishment of diagnosis by using a proper diagnostic method. Delay in diagnosis may result in serious morbidity and mortality. One of our patients with late testicular TB had additional vertebral and psoas involvement at the time of diagnosis (30). In our patient group, gastrointestinal system was the most frequently involved system. In a comparative study of PTB and EPTB on a total of 474 cases (48.5% EPTB and 51.5% PTB), Sreeramareddy et al. (11) reported that patients with EPTB had 42.6% lymph node involvement, 14.8% peritoneal and/or intestinal involvement, and 12.4% bone and/or joint involvement. Some rare EPTB cases had 7.2% miliary, 7.2% meningeal/brain, 4.8% skin, 2.9% genital and 2.4% laryngeal involvement (11). The rate of EPTB is variable (3,4,9-11). This variation may be related to social and environmental factors as well as to the center where the study is conducted. Our study was conducted at a chest diseases center where PTB cases are frequently referred. This may be the cause of our limited number of EPTB cases. The rate of co-existence of PTB and EPTB has been reported to range from 16 to 34% (3,6,11,12). This rate was 16% in our study. It has been reported that treatment longer than 9 months has no additional advantage, and that long-term treatment reduces patient compliance and increases costs (31,32). Our study has some limitations: The data were obtained retrospectively from patient files. Some patients lacked data on lifestyle. Thus, in some cases, it was not possible to study the effects of social, ethnic, economic, and environmental factors and therefore the reasons for delayed treatment. In addition, since this study was conducted on a small group of cases and at a tertiary hospital, it does not reflect the situation in the whole population. Prospective future studies are required to overcome these limitations.

CONCLUSION

In conclusion, as seen in our patient group, TB is a systemic infection that can involve any organ in the body. Delayed diagnosis and treatment of TB result in serious morbidity and mortality. We think that EPTB is overlooked in cases with no PTB. In cases without specific symptoms and findings, suspicion of EPTB is the most important step toward definitive diagnosis. In our patient group, patients exhibited organ-specific symptoms, frequently along with symptoms expected in TB. Particularly in female patients, the presence of these symptoms with a history of contact with TB and TST-positivity should lead the clinician to suspect TB even in the absence of PTB. The suspicion of TB will lead to early diagnosis with diagnostic algorithm and treatment that decreases costs, mortality and morbidity.

Ethics

Ethics Committee Approval: Ethics committee approved. (İstanbul Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, 13.11.2015/7).

Informed Consent: Retrospective study.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G., M.Y., E.A., Concept: S.G., Ö.S., Design: S.G., B.B.A.D., Data Collection or Processing: O.A., E.A.Ö., Analysis or Interpretation: S.G., M.Y., Literature Search: S.G., E.U.B., Writing: S.G., M.Y.

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REFERENCES

1. World Health Organization. Global Tuberculosis Report 2014. Available from: URL: http://www.who.int/tb/publications/global_report/gtbr14_main_text.pdf?ua=1.
2. The ministry of health of Turkey health. Tuberculosis Report 2012. URL: www.tuberkuloz.thsk.gov.tr.
3. Guler SA, Bozkus F, Inci MF, Kokoglu OF, Ucmak H, Ozden S, et al. Evaluation of Pulmonary and Extrapulmonary Tuberculosis in Immunocompetent Adults: A Retrospective Case Series Analysis. Med Princ Pract 2015;24:75-9.
4. Musellim B, Erturan S, Sonmez Duman E, Ongen G. Comparison of extrapulmonary and pulmonary tuberculosis cases: factors influencing the site of reactivation. Int J Tuberc Lung Dis 2005;9:1220-3.
5. Sunnetcioglu A, Sunnetcioglu M, Binici I, Baran AI, Karahocagil MK, Saydan MR6. Comparative analysis of pulmonary and extrapulmonary tuberculosis of 411 cases. Ann Clin Microbiol Antimicrob 2015;14:34.
6. Tavusbay N, Aksel N, Özsöz A. Epidemiologic, clinical and laboratory features of cases with extrapulmonary tuberculosis. İzmir Göğüs Hastanesi Dergisi 2008;22:27-34.
7. Turunç T, Habeşoğlu MA, Demiroğlu YZ, Karataşli M, Sen N, Ermiş H, et al. Comparative evaluation of 113 cases with severe and mild forms of extrapulmonary tuberculosis. Mikrobiyol Bul 2008;42:399-406.
8. Antony SJ, Harrell V, Christie JD, Adams HG, Rumley RL. Clinical differences between pulmonary and extrapulmonary tuberculosis: a 5-year retrospective study. J Natl Med Assoc 1995;87:187-92.
9. Demiralay R. Comparison of the Clinical and Epidemiological Characteristics of Pulmonary and Extrapulmonary Tuberculosis. Tuberk Toraks 2002;50:264-71
10. Fader T, Parks J, Khan NU, Manning R, Stokes S, Nasir NA. Extrapulmonary tuberculosis in Kabul, Afghanistan: a hospital-based retrospective review. Int J Infect Dis 2010;14:e102-10.
11. Sreeramareddy CT, Panduru KV, Verma SC, Joshi HS, Bates MN. Comparison of pulmonary and extrapulmonary tuberculosis in Nepal - a hospital-based retrospective study. BMC Infect Dis 2008;8:8.
12. Lin JN, Lai CH, Chen YH, Lee SS, Tsai SS, Huang CK, et al. Risk factors for extrapulmonary tuberculosis compared to pulmonary tuberculosis. Int J Tuberc Lung Dis 2009;13:620-5.
13. Sherif MM, Schauer CK. Multifocal Cutaneous and Osseous Tuberculosis. Int J Infect Dis 2015;37:11-3.
14. Sharma V, Chhabra P, Rana SS, Bhasin DK. Pancreatic tuberculosis: Look at the kidney! Dig Liver Dis 2015;47:e1.
15. Lombardi R, Pelusi S, Airaghi L, Fargion S. Extrapulmonary tuberculosis: an unusual presentation in an immunocompetent patient. BMJ Case Rep 2015;2015.
16. Lee KJ, Yoo JS, Jeon H, Cho SK, Lee JH, Ha SS, et al. A Case of Splenic Tuberculosis Forming a Gastro-splenic Fistula. Korean J Gastroenterol 2015;66:168-71.
17. Gupta N, Dass A, Goel N, Tiwari S. Tuberculous Otitis Media Leading to Sequentialib Bilateral Facial Nerve Paralysis. Iran J Otorhinolaryngol 2015;27:231-7.
18. Pandit VR, Shubha S, Rohit V, Vikas M, Vandana KE, Ashwini K, et al. Pott's spine with 'bird nest' appearance. Int J Infect Dis 2010;14 Suppl 3:e390-1.
19. Karan MA, Erten N, Taşçıoğlu C, Kazancıoğlu R, Kaysı A. Extrauplmonary Tuberculosis: 5 case report. Klimik Derg 1995;8:68-70.
20. Organization WH. World Health Organization. Diagnostic and Treatment Delay in Tuberculosis. 2006. URL: http://applications.emro.who.int/dsaf/dsa710.pdf.
21. Menzies D. Interpretation of repeated tuberculin tests. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. Am J Respir Crit Care Med 1999;159:15-21.
22. Gunal S, Yang Z, Agarwal M, Koroglu M, Arıcı ZK, Durmaz R. Demographic and microbial characteristics of extrapulmonary tuberculosis cases diagnosed in Malatya, Turkey, 2001-2007. BMC Public Health 2011;11:154.
23. Chan-Yeung M, Noertjojo K, Chan SL, Tam CM. Sex differences in tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2002;6:11-8.
24. Borgdorff MW, Nagelkerke NJ, Dye C, Nunn P. Gender and tuberculosis: a comparison of prevalence surveys with notification data to explore sex differences in case detection. Int J Tuberc Lung Dis 2000;4:123-32.
25. Kolappan C, Gopi PG. Tobacco smoking and pulmonary tuberculosis. Thorax 2002;57:964-6.
26. Leung CC, Yew WW, Chan CK, Tam CM, Lam CW, Chang KC, et al. Smoking and tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2003;7:980-6.
27. Akbaba B, Baran A, Yalçinsoy M, Güngör S, Akkaya E. [Two sisters with breast tuberculosis]. Tuberk Toraks 2007;55:395-9.
28. The ministry of health of Turkey health. Tuberculosis diagnosis and treatment Guideline 2011. URL: www.tuberkuloz.thsk.gov.tr.
29. Gonzalez OY, Adams G, Teeter LD, Bui TT, Musser JM, Graviss EA. Extrapulmonary manifestations in a large metropolitan area with a low incidence of tuberculosis. Int J Tuberc Lung Dis 2003;7:1178-85.
30. Yalçınsoy M, Güngör S, Akkaya E, Bilgin S, Akkütük E, Sırmalı M, et al. [Progress of treatment delayed testicular tuberculosis: one case]. Tuberk Toraks 2013;61:255-7.
31. Syed FF, Mayosi BM. A modern approach to tuberculous pericarditis. Prog Cardiovasc Dis 2007;50:218-36.
32. Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603-62.

ORIGINAL ARTICLE

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Calculation of Embryo/Fetus Dose in Pregnant Thyroid Patients Who Have Accidentally Received Radioiodine

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Abstract

Objective: The aim of this study was to calculate the embryo/fetus dose in pregnant patients who have accidentally received radioiodine (^{131}I) and to evaluate the termination of pregnancy by giving teratological advice to the family.

Methods: In this study, fetus dose was calculated in 16 patients who were referred to our department following the application of ^{131}I radioisotope for diagnosis and treatment in different nuclear medicine centers.

Results: Mean embryo/fetus dose of three pregnant patients, who received 0.37 MBq (10 µCi) ^{131}I orally for thyroid uptake test, was calculated as 0.063 mGy. For uptake/scintigraphy test, 1.85 MBq (0.05 mCi) ^{131}I was applied to six patients, and the calculated mean fetal dose was 0.13 mGy and fetal thyroid dose was 1073 mGy (1.073 Gy). Mean embryo/fetus dose of three patients who received mean 185 MBq (5 mCi) ^{131}I orally for whole body scintigraphy was calculated as 13.2 mGy. One of two patients with hyperthyroidism was administered 370 MBq (10 mCi) ^{131}I orally and the embryo/fetus dose was calculated as 26.64 mGy and fetal thyroid dose was calculated as 215340 mGy (215.34 Gy). The other patient with hyperthyroidism received 481 MBq (13 mCi) ^{131}I and embryo/fetus dose was calculated as 34.63 mGy. One of two patients diagnosed with thyroid cancer received 3700 MBq (100 mCi) ^{131}I and the embryo/fetus dose was calculated as 266.64 mGy. The other patient with thyroid cancer received 5555 MBq (150 mCi) ^{131}I at 15th gestational week, and fetus dose was calculated as 377.8 mGy and fetal thyroid dose was calculated as 3221.9 Gy.

Conclusion: Diagnostic ^{131}I administration before the 10th week of pregnancy induces insufficient radiation dose for termination of pregnancy. Whilst, the embryo/fetus dose in pregnant women with high doses of ^{131}I rise up to more than 100 mGy and these cases shoulde be therefore evaluated in terms of termination of pregnancy.

Keywords: Fetus dose, fetal thyroid dose, radiation dose

INTRODUCTION

Radioiodine (^{131}I) has been used for many years in the diagnosis and treatment of hyperthyroidism (HTT) and thyroid cancer. Thyroid uptake test (TU) is performed for diagnostic purposes and/or scintigraphic imaging, with using 365 keV using 365 keV energy gamma rays following oral administration of low dose ^{131}I, such as 0.37-1.85 MBq (10-50 µCi). In addition to gamma rays, ^{131}I emits beta particles with 606 keV, which are used for treatment. 222-1110 MBq (6-30 mCi) is used for the HTT and 1110-7400 MBq (30-200 mCi) is used for the treatment of thyroid cancer (1). Regarding Turkey Atomic Energy Authority radiation protection legislation, patients who underwent therapy with more than 600 MBq (16.2 mCi) at a time should be isolated in radionuclide therapy rooms in nuclear medicine clinics until the radiation dose rate decreases to <30 µsv/h at 1 meter (2). In all radionuclide applications for diagnosis and treatment, pregnancy status of female patients of reproductive age are questioned and pregnancy test is requested in every suspicious case. Despite these precautions, ^{131}I treatment may be applied to the pregnant women by accident in the first 10 days of pregnancy or in case of false negative pregnancy test results. In these applications, ^{131}I reaches the placenta by metabolic pathways and irradiates the embryo/fetus. Fetal thyroid gland develops starting from the 10th week of pregnancy. The ^{131}I radionuclide

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concentrates in the thyroid gland of the fetus as well as in the mother's thyroid gland and participates in hormogenesis such as the non-radioactive iodine element. Therefore, ^{131}I causes high fetal thyroid dose especially with beta rays during its stay in fetal thyroid gland (3,4). In radiopharmaceutical applications, the radiation dose to which the embryo/fetus is exposed and the fetal thyroid dose can be calculated using various phantoms. The most commonly used of these phantoms are pregnant women phantoms developed by Stabin (5). Stabin's pregnant women models mimic the first period of pregnancy, 3 months, 6 months and 9 months of pregnancy. Russell et al. (6) calculated the radiation doses delivered to the embryo/fetus by radiopharmaceuticals used in nuclear medicine by using Stabin's pregnant female phantoms and presented the results in tables as mGy/MBq dose units. It is known that radiation has deterministic effects on embryo/fetus in prenatal period, including intrauterine death, organ malformations, growth developmental retardation, and mental retardation. To see these effects, the radiation dose to which the embryo/fetus is exposed must exceed a certain threshold. It has been shown that the cumulative radiation dose that may be harmful to the embryo/fetus is 50 mGy (5 rad), but if the radiation exposure is below this amount during the entire pregnancy period, the embryo/fetus is far from deterministic effects and the risk of congenital anomalies does not increase significantly (7-11). There is no threshold dose in the theory of radiation-induced cancer, known as stochastic effect. In general, it is accepted that the embryo/fetus is more sensitive to ionised radiation and protective measures have been proposed (6). According to the generally accepted approach to termination of pregnancy, if the embryo/fetus is exposed to radiation doses higher than 100 mGy, the family should be given teratological counseling, and accurate, realistic and scientific information should be provided on the possible effects of ionized radiation and the risks to the baby. The decision to terminate the pregnancy should be made by the parents in accordance with the information provided by medical experts (12). If the embryo/fetus is exposed to radiation doses of more than 100 mGy between the 10th and 25th weeks of pregnancy, termination of pregnancy is recommended due to the increased risk of fetal malformation, central nervous system damage, and growth and developmental retardation (7,13). Stochastic effects on the embryo/fetus have been reported to occur at doses of 100-200 mGy (14,15). The aim of this study was to determine the embryo/fetus dose and to evaluate the termination status of the pregnant women who underwent ^{131}I in nuclear medicine centers.

METHODS

The study was initiated following the approval of the İstanbul University Cerrahpaşa Faculty of Medicine Ethics Committee (approval number: 219488, dated: 09/07/2015).

Patient Groups

According to the procedure in Cerrahpaşa Faculty of Medicine, pregnant women who accidently underwent radioactive investigation apply to the department of medical genetics. Patients whose gestational age is determined here by ultrasonography are referred to the department of nuclear medicine for calculation of the embryo/fetus dose and then referred back to the department of medical genetics. In this study, the embryo/fetus dose of 16 patients who underwent diagnostic and therapeutic 131I at different nuclear medicine centers between July 2015 and June 2017 was computed in the nuclear medicine department. Of these patients, three patients with HTT underwent diagnostic 0.37 MBq (10 µCi) ^{131}I for TU, six patients who underwent thyroidectomy received 1.85 MBq (0.05 mCi) ^{131}I for TU scintigraphy (TUS), three patients received 185 MBq (5 mCi) ^{131}I for whole body scintigraphy (WBS), and two patients received therapeutic ^{131}I for HTT and two patients received therapeutic ^{131}I for thyroid cancer treatment (TCT). On the day of radiotherapy, 15 of the patients were in the first 3 months of pregnancy and one of them was in the 4th month.

Calculation and Evaluation of Embryo/Fetus Dose/Fetal Thyroid Dose

The radiation doses (mGy/MBq) given to the embryo/fetus by the radiopharmaceuticals administered to the mother during various periods of pregnancy were calculated from phantoms by Russell et al. (6) (Table 1) (12). Fetal thyroid gland develops starting from the 10th week of pregnancy. Taking into account this criterion in the calculation of fetus doses in our study, fetal thyroid dose was also calculated in fetuses with at least 10 weeks of gestation. The calculation of fetal thyroid dose was based on the table published by Watson (3) (Table 2). In accordance with

Table 1. Doses per unit activity (MBq) given to the embryo/fetus (mGy) from radioiodine 131 radionuclide administered to the mother (6)

Radiopharmaceutical	Early period	3 months	6 months	9 months
^{131}I sodium iodide	7.2x10-2 mGy/MBq	6.8x10-2 mGy/MBq	2.3x10-1 mGy/MBq	2.7x10-1 mGy/MBq

^{131}I: Radioiodine 131

the routine application protocol of our study team, after the embryo/fetus dose is calculated in the department of nuclear medicine, the final report is submitted to the expectant mother and then directed to the department of medical genetics. Cases with embryo/fetus and fetal thyroid doses more than 100 mGy are re-referred to the outpatient clinic of the department of medical genetics. The medical genetic specialist determines the other teratogenic factors of the pregnant woman and sends the risk report to the obstetrician. As a result, the termination proposal is made by the physician to the parents and the decision is made by the parents.

Statistical Analysis

The data in this study were evaluated in detail and no statistical analysis was performed.

RESULTS

The study cohort consisted of pregnant women who underwent diagnostic and therapeutic nuclear medicine applications for thyroid diseases in different centers around Turkey. Mean embryo/fetus dose of three patients, who received 0.37 MBq (10 µCi) ^{131}I orally for TU test, was calculated as 0.063 mGy. Fetal thyroid doses were not calculated since thyroid formation did not occur because the gestational age of the patients was less than 10 weeks. In six patients who underwent total thyroidectomy with the diagnosis of thyroid cancer, 1.85 MBq (50 µCi) ^{131}I was administered orally for the diagnosis of residual thyroid tissue and TUS was performed for diagnostic purposes. Three of these patients had gestational age less than 10 weeks and two of them had gestational age more than 10 weeks. The calculated mean fetal dose was 0.13 mGy and fetal thyroid dose was 1073 mGy (1.073 Gy). In patients undergoing total thyroidectomy and ^{131}I therapy, WBS is usually performed at 6-12 months after ^{131}I therapy for ablation control and metastasis research. In this diagnostic study, 185 MBq (5 mCi) ^{131}I was administered orally to each of the three patients. Since the gestational age of the patients was less than 10 weeks, only embryo/fetus doses were calculated and the mean value was 13.2 mGy. The gestational age of one of the two patients undergoing HTT was 11 weeks-5 days, and 481 MBq (13 mCi) ^{131}I was administered orally to this patient. The fetal dose was 26.64 mGy and the fetal thyroid dose was 215340 mGy (215.34 Gy). Since the other patient with HTT had a 3 week-0 day pregnancy, only the embryo/fetus dose was calculated and found as 34.63 mGy. One of the two patients who underwent TCT received 3700 MBq (100 mCi) ^{131}I and the embryo/fetus dose was 266.64 mGy. The patient who received 5555 MBq (150 mCi) ^{131}I was 15 weeks pregnant, and the fetus dose was 377.8 mGy and the fetus thyroid dose was 3221.9 Gy (Table 3). Following labor, 13 out of 16 women were followed up. One woman who had TU and two women who had TUS could not be followed up. Of the 13 women who were followed up, two women who underwent TU had vaginal birth with healthy babies, and their thyroid hormone tests and mental performance tests were found to be normal. Two of six women who had TUS could not be followed up. Radiotherapy was planned for breast cancer in one of the four women who were followed up and medical abortion was performed. The remaining three women had vaginal birth, and one of the babies had hypothyroidism and the other two babies had normal thyroid hormone tests and mental performance tests. One of the three women who had WBS examination delivered stillbirth in the 24th week of pregnancy and the other two had healthy babies with vaginal birth. One of the two women who underwent HTT had medical abortion due to high fetal thyroid dose exposure, the other gave birth to a healthy baby with normal delivery, and thyroid hormone tests and mental performance tests of the baby were found to be normal. Two women who had underwent TCT underwent medical abortion due to high fetal dose and high fetal thyroid dose. The mean values of the calculated embryo/fetus doses are shown in Figure 1. In ^{131}I applications, it was determined that embryo/fetus dose was low in patients with gestational age less than 10 weeks and fetal thyroid dose increased significantly in gestational age more than 10 weeks. It was observed that both embryo/fetus dose and fetal thyroid dose were at very high levels due to high iodine activities applied for TCT (Figure 2).

Table 2. Doses per unit activity (MBq) given to the embryo/fetus (mGy) from iodine radioisotopes administered to the mother (3)

Gestational age (months)	^{123}I	^{124}I	^{125}I	^{131}I
3	2.7	24	290	230
4	2.6	27	240	260
5	6.4	76	280	580
6	6.4	100	210	550
7	4.1	96	160	390
8	4.0	110	150	350
9	2.9	99	120	270

^{123}I: Radioiodine 123, ^{124}I: Radioiodine 124, ^{125}I: Radioiodine 125, ^{131}I: Radioiodine 131

DISCUSSION

The embryo/fetus is highly sensitive to radiation. The ^{131}I radionuclide used in the diagnosis and treatment of thyroid diseases is an important risk to the embryo/fetus when taken into the body of the pregnant woman because of its characteristics

such as high energy beta and gamma rays and relatively long physical half-life. It is recommended that fetal thyroid dose be calculated in order to determine the risk ratio (3). It has been known for many years that fetal thyroid develops at the 10th week of pregnancy and it concentrates the iodine element (16). Stabin, (17) one of the authorities on this issue, reported that thyroid functions may be completely lost in higher doses as well as thyroid dysfunction may be observed as a result of high dose exposure of fetal thyroid during pregnancy. It is known that the ^{131}I applied to the expectant mother passes through the placenta by active transport mechanism like the non-radioactive iodine element and mixes with the fetal blood and that the iodine concentration in the fetal blood is 75% in the mother's blood. During thyroid hormone synthesis using the ^{131}I element, fetal thyroid tissue is exposed to radiation. While beta rays of ^{131}I give high radiation dose to fetal thyroid tissue, gamma rays give radiation dose to both fetal thyroid and whole fetus (18). The radiation dose delivered to a fetal thyroid tissue by ^{131}I applied to a 12 week old pregnant woman was evaluated as 350 mGy/MBq by Roedler (19) and as 220 mGy/MBq by Johnson (20). In our study, the calculated fetal thyroid dose was 230 mGy/MBq in an 11 week pregnant woman. After ^{131}I is administered to a woman with unknown pregnancy, dosimetry is required to determine the radiation dose received by the embryo/fetus.

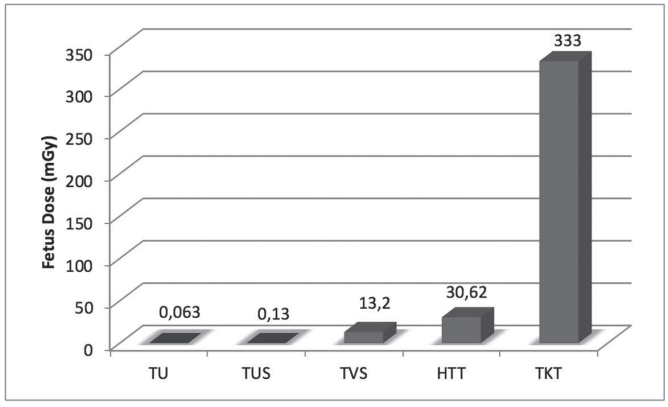

Figure 1. Distribution of mean embryo/fetus doses in diagnostic and therapeutic radioiodine 131 administration

TU: Thyroid uptake, TUS: Thyroid uptake scintigraphy, HTT: Treatment of hyperthyroidism, TCT: Thyroid cancer treatment

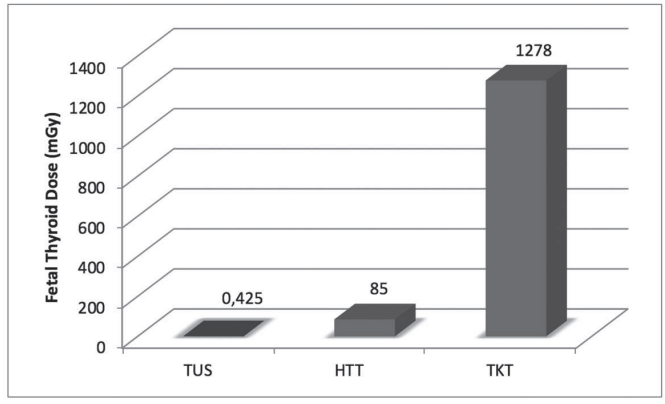

Figure 2. Distribution of mean fetal thyroid doses in diagnostic and therapeutic radioiodine 131 administration

TUS: Thyroid uptake scintigraphy, HTT: Treatment of hyperthyroidism, TCT: Thyroid cancer treatment

Table 3. Embryo/fetus and fetal thyroid doses calculated after administration of radioiodine 131

	Patient no application purpose	Dose applied MBq (mCi)	Gestational age (week, day)	Embryo/fetus dose (mGy)	Fetal thyroid dose (mGy)	Pregnancy follow up
Low dose (diagnostic)	1. TU	0.37 (0.01)	3 w, 3 d	0.063	-	Live, healthy birth
	2. TU	0.37 (0.01)	3 w, 1 d	0.063	-	Live, healthy birth
	3. TU	0.37 (0.01)	6 w, 2 d	0.063	-	Out of follow-up
	4. TUS	1.85 (0.05)	2 w, 5 d	0.13	-	Medical abortion Live, healthy birth
	5. TUS	1.85 (0.05)	11 w, 4 d	0.12	425 (0.425 Gy)	Out of follow-up
	6. TUS	1.85 (0.05)	2 w, 5 d	0.13	-	Live, healthy birth
	7. TUS	1.85 (0.05)	10 w, 3 d	0.12	425 (0.425 Gy)	Out of follow-up
	8. TUS	1.85 (0.05)	5 w, 5 d	0.13	-	Live, healthy birth
	9. TUS	1.85 (0.05)	3 w, 5 d	0.13	-	Live, healthy birth
	10. WBS	185 (5)	5 w, 2 d	13.2	-	Stillbirth
	11. WBS	185 (5)	6 w, 3 d	13.2	-	Live, healthy birth
	12. WBS	185 (5)	2 w, 4 d	13.2	-	
High dose (treatment)	11. HTT	370 (10)	11 w, 5 d	26.64	85100 (85.1 Gy)	Medical abortion
	12. HTT	481 (13)	3 w, 0 d	34.63	-	Live, healthy birth
	13. TCT	3700 (100)	2 w, 3 d	266.4	-	Medical abortion
	14. TCT	5555 (150)	13 w, 0 d	377.8	1277650 (1277.6 Gy)	Medical abortion

TU: Thyroid uptake, TUS: Thyroid uptake scintigraphy, WBS: Whole body scintigraphy, HTT: Treatment of hyperthyroidism, TCT: Thyroid cancer treatment, w: Week, d: Day

In Report 54 of the National Council on Radiation Protection and Measurements, fetal dose exposures below 50 mGy (5 rad) are reported to be negligible in terms of congenital risk when compared to natural risks in pregnancy (21). This organization reported that if the embryo/fetus dose is greater than 150 mGy (15 rad); the risk of malformation may be uncontrollably high. Otake et al. (22) examined the effects of the atomic bomb on Japanese pregnant women and reported that embryo/fetus was the most sensitive to radiation between 8th and 15th weeks of pregnancy. In the Committee on the Biological Effects of Ionizing Radiation V report evaluating the effects of radiation on fetus, it was reported that the radiation dose to be given to the fetus by ^{131}I radionuclide with 3700-7400 MBq activity for therapeutic purposes by accident between 8th and 15th weeks of pregnancy will exceed the threshold value (23). The International Commission on Radiological Protection-84 report stated that if the fetal dose is >10 mGy, the risk of leukemia and cancer may increase by 40%, and that if the fetus dose is 100-1000 mGy, pregnancy should be terminated (24). Maxon and Smith (25) reported that the total dose required to ablate residual thyroid tissue in patients undergoing total thyroidectomy for TCT was 300 Gy. If a high-dose ^{131}I is administered to an expectant mother at the 10th gestational week, the fetal thyroid dose exceeds the 300 Gy limit in most cases. In addition, thyroid gland is evaluated in the critical organs group in terms of radiation dose and the tolerance dose has been reported as 20 Gy (26-28). In such cases, fetal thyroid dose should be determined and teratological counseling should be given to the family. In addition, pregnancy test should be performed before radioactive applications in any suspicious cases. If ^{131}I is applied to a pregnant woman by accident in diagnostic tests such as TU and/or TUS, it is useful to make the patient drink plenty of water to accelerate urinary excretion (29).

CONCLUSION

According to the results of this study, it is concluded that patient-specific embryo/fetus dose estimation is necessary for pregnant women who received radioiodine in pregnant women who received ^{131}I radionuclide, ^{131}I which is applied for diagnostic purposes before the 10th week of pregnancy will not deliver radiation dose enough to cause anomalies in the embryo alone, and that ^{131}I radionuclide administered in the treatment of HTT and thyroid cancer after the 10th week of pregnancy can be an indication for medical abortion due to increasing fetus dose above 100 mGy and fetal thyroid dose above 20 Gy.

Ethics

Ethics Committee Approval: The study was initiated following the approval of the İstanbul University Cerrahpaşa Faculty of Medicine Ethics Committee (approval number: 219488, dated: 09/07/2015).

Informed Consent: Informed consent from was patient.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Concept: M.D., İ.Ç., M.S., Design: M.D., M.S, M.A., L.U.B., Data Collection or Processing: N.Y., N.İ., M.B.D., Analysis or Interpretation: L.U.B., M.B.D., Literature Search: M.D., İ.Ç., M.A., Writing: M.D., L.U.B., M.A.

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REFERENCES

1. Uslu Beşli L, Demir M. Radiation in Thyroid Cancer Patients. Hojjat Ahmedzaedfar, editors. Thyroid cancer-Advanced in Diagnosis and Therapy. Rejeka, Croatia: Intech 2016,229-45.
2. Türkiye Atom Enerjisi Kurumu (TAEK) Radyasyon Güvenlik Yönetmeliği, 2000.
3. Watson EE. Radiation absorbed dose to the human fetal thyroid. In :Fifth International Radiopharmaceutical Dosimetry Symposium. Oak Ridge, TN: Oak Ridge Associated Universities 1992,170-187.
4. Stabin MG, Siegel JA, Sparks RB, Eckerman KF, Breitz HB. Contribution to red marrow absorbed dose from total body activity: a correction to the MIRD method. J Nucl Med 2001;42:492-8.
5. Stabin MG. Radiation dose concerns for the pregnant or lactating patient. Semin Nucl Med 2014;44:479-88.
6. Russell JR, Stabin MG, Sparks RB, Watson E. Radiation absorbed dose to the embryo/fetüs from radiopharmaceuticals. Health Phys 1997;73:756-69.
7. Barent RL. Saving lives and changing family histories: appropriate counseling of pregnant women and men and women of reproductive age, concerning the risk of diagnostic radiation exposures during and before pregnancy. Am J Obstet Gynecol 2009;200:4-24.
8. International Commission on Radiological Protection. Pregnancy and Medical Radiation. ICRP Publication 84. Ann ICRP 2000;30:1-43.
9. Wagner LK, Lester RG, Saldana LR, editors. Exposure of the pregnant patient to diagnostic radiations. 2nd ed. Madison: Medical Physics Publishing Corporation;1997.
10. American Coolege of Radiology. AcoR 05-05 bylaws. Reston, Va: American Collage of Radiology, 2005.
11. Brent RL. Utilization of juvenile animal studies to determine the human effects and risks of environmental toxicants during postnatal developmental stages. Birth Defects Res B Dev Reprod Toxicol 2004;71:303-20.
12. Stabin MG. Radiation dose and risks to fetus from nuclear medicine procedures. Physica Medica 2017;43,190-8.

13. Hall EJ, Giarccia AJ. Effect of radiation on the embryo and fetüs. Radiobiology fort he radiologist. 6th.ed. Philadelphia: Lippincott. 2006;168-80.

14. Ratnapalan S, Bona N, Chandra K, Koren G. Physicians' perceptions of teratogenic risk associated with radiography and CT during early pregnancy. AJR Am J Roentgenol 2004;182:1107-9.

15. Preston DL, Cullings H, Suyama A, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors exposed in utero or as young children. J Natl Cancer Inst 2008;100:428-36.

16. Cloutier RJ, Smith SA, Watson EE, Snyder WS, Warner GG. Dose to the fetus from radionuclides in the bladder. Health Phys 1973;25:147-61.

17. Stabin MG, Watson EE, Marcus CS, Salk RD. Radiation dosimetry for the adult female and fetüs from iodine-131 administration in hyperthyroidism. J Nucl Med 1991;32:808-13.

18. Watson EE. Radiation absorbed dose to the human fetal thyroid. Fifth International Radiopharmaceutical Dosimetry Symposium,May 7-10,1992 Oak Ridge, Tennessee-USD.

19. Roedler HD. Assessment of fetal activity concentration and fetal dose for selected radionuclides based on animal and human data. Age-related Factors in Radionuclide Metabolism and Dosimetry. GB Gerber, H Metivier, and H Smith, editors. Dordrecht: Martinus Nijh off Publishers; 1987.p.327-37.

20. Johnson JR. A review of age dependant radioiodine dosimetry. Agerelated Factors in Radionuclide Metabolism and Dosimetry. GB Gerber, H Metivier, and H Smith, editors, Dordrecht: Martinus Nijhoff Publishers; 1987.p.249-59.

21. National Council on Radiation Protection and Measurements. Medical radiation exposure of pregnant and potentially pregnant women. NCRP report no. 54. Bethesda, MD: National Council on Radiation Protection and Measurements; 1977.

22. Otake M, Yoshimaru H, Schull W. Severe mental retardation among the prenatally exposed survivors of the atomic bombing of Hiroshima and Nagasaki: a comparison of the T65DR and DS86 dosimetry systems. RERF TR 16-87. Radiation Effects Research Foundation, Japan, 1988.p.40.

23. Committee on the Biological Effects of Ionizing Radiations. Health effects of exposure to low levels of ionizing radiation, BEIR V. Washington, DC: National Academy Press; 1990.

24. International Commission on Radiological Protection. Pregnancy and medical radiation. Ann ICRP 2000;30,1-43.

25. Maxon HR, Smith HS. Radioiodine-131 in the diagnosis and treatment of metastatic well differentiated thyroid cancer. Endocrinol Metab Clin North Am 1990;19:685-718.

26. Tunio MA, Al Asiri M, Bayoumi Y, Stanciu LG, Al Johani N, Al Saeed EF. Is thyroid gland an organ at risk in breast cancer patients treated with locoregional radiotherapy? Results of a pilot study. J Cancer Res Ther 2015;11:684-9.

27. Alterio D, Jereczek-Fossa BA, Franchi B, D'Onofrio A, Piazzi V, Rondi E et al. Thyroid disorders in patients treated with radiotherapy for head-and-neck cancer: a retrospective analysis of seventy-three patients. Int J Radiat Oncol Biol Phys 2007;67:144-50.

28. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109-22.

29. Sabbir Ahmed AS, Demir M, Yasar D, Uslu I. Quantification of absorbed doses to urine bladder depending on drinking water during radioiodine therapy to thyroid cancer patients: a clinical study using MIRDOSE3. Nucl Med Commun 2003;24:749-54.

ORIGINAL ARTICLE

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Evaluation of Hysteroscopy in Infertile Patients

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Abstract

Objective: The aim of this study was to evaluate the hysteroscopy results in infertile patients and to compare the clinical pregnancy, live birth and abortion rates between patients with uterine cavity abnormalities treated with operative hysteroscopy and patients with normal uterine cavity.

Methods: Three hundred and nineteen patients who underwent hysteroscopy for infertility between January 2010 and December 2015 were included in the study. The patients were divided into two main groups: diagnostic and operative. The patients who had normal uterine cavity in exploration and who did not require surgical intervention were referred as diagnostic hysteroscopy group. Patients who underwent surgical intervention during the procedure were named as operative hysteroscopy group. The operative hysteroscopy group was divided into groups as endometrial polyp, submucous myoma, septum, adhesions and T-shaped uterus. Demographic data, laboratory parameters and pregnancy outcomes after hysteroscopy were recorded. Clinical pregnancy, live birth and abortion rates were compared between the groups.

Results: The demographic and laboratory characteristics of the diagnostic (n=74) and operative hysteroscopy (n=245) groups were similar. After operative hysteroscopy, 53.9% of the patients had clinical pregnancy and 41.3% of them had live birth. In the diagnostic hysteroscopy group, the clinical pregnancy rate was 55.2% and the live birth rate was 41.7%. There was no significant difference between the two groups in terms of clinical pregnancy and live birth rates. In addition, there was no difference between the two groups in terms of pregnancy acquisition methods and mean duration of conception. In the operative hysteroscopy subgroups, the highest rates of clinical pregnancy and live birth were in patients undergoing endometrial polyp and septum resection, and abortion rates were highest in T-shaped uterus and septum resection groups.

Conclusion: We concluded that treatment of uterine cavity pathologies with operative hysteroscopy in infertile patients provided similar clinical pregnancy and live birth rates to patients who have normal uterine cavity.

Keywords: Hysteroscopy, infertility, pregnancy outcomes

INTRODUCTION

Infertility is the condition in which a couple in reproductive ages cannot achieve pregnancy despite regular unprotected sexual intercourse for one year below the age of 35 and for more than 6 months above the age of 35 (1). Appropriate selection of the tests to be performed in this case, which affects approximately 10-15% of all reproductive couples, is extremely important in both diagnosis and treatment (2). Infertility is a process that demolishes families socioeconomically and psychologically. The main causes of infertility are ovulatory dysfunction (20-40%), tubal and peritoneal pathology (30-40%), male factor (30-40%), unexplained infertility (10%) and uterine pathologies (10-15%), and intrauterine pathologies are one of the reasons that can be treated surgically (3). It is known that the frequency of intrauterine pathologies increases in infertile patients. The presence of intrauterine pathologies negatively affects fertility by decreasing the receptivity and implantation success (4). The methods used to detect these pathologies are ultrasonography (US), saline infusion sonography (SIS), hysterosalpingography (HSG) and hysteroscopy (HS). HS is a widely used method in the diagnosis and treatment of intracavitary pathologies in gynecology practice. In addition to providing direct observation of the cervical canal and uterine cavity, HS is a preferred technical method in the evaluation of infertile patients in

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recent years because it is a minimally invasive procedure, has low complication rate, allows for diagnostic and therapeutic interventions, and has high sensitivity and specificity (5). The aim of this study was to evaluate the results of HS applied to infertile patients and to compare the clinical pregnancy, live birth and abortion rates of patients treated with operative HS for intrauterine pathologies with patients with normal cavities.

METHODS

Ethics committee approval was received for this study from the Ethics Committee of İstanbul University Cerrahpasa Faculty of Medicine (approval number: 135378). Patient files were reviewed retrospectively. The study included 319 infertile patients who underwent diagnostic HS for indications such as polyps, submucous myoma, suspicion of septum, adhesion, uterine deformity, recurrent implantation failure (two or more failed embryo transfer cycles) and infertility treatment between January 2010 and December 2015 in İstanbul University Cerrahpaşa Faculty of Medicine, Department of Obstetrics and Gynecology. Age, obstetric history (pregnancy, birth, abortion and optional curettage count), height, weight, body mass index (BMI), duration of infertility, etiology of infertility, previous treatment for infertility, US findings, SIS and HSG findings if performed, HS indications, HS findings, pregnancy acquisition method (spontaneous or assisted reproductive techniques), presence of systemic or gynecological diseases, history of previous gynecological intervention, drug use, and smoking and alcohol use were recorded. In addition, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin, thyroid stimulating hormone (TSH) and anti-mullerian hormone (AMH) levels measured between the 3rd and 5th days of menstrual cycle were recorded. The visualization of endocervical canal, uterine cavity and both tubal ostium was determined as a criterion for a HS to be accepted as sufficient. Patients over 40 years of age, with a history of recurrent pregnancy loss, who were reported to have malignancy as a result of pathological examination and patients who could not be operated due to insufficient cervical dilatation during HS were excluded. In our clinic, HS procedure is performed on the 8th-11th days of the menstrual cycle after menstrual bleeding under general anesthesia in the operating room. The instruments required for HS include a) 30°, size 4 mm, 30 cm long Olympus (Storz®) hysteroscope, b) metal sheath, size 5.5 mm, with working channels for distension, irrigation and semirigid operating instruments, c) computer with 37 inch Sony® (Japan) monitor, camera and DV studio AVIO program with special recording for each patient, d) cuff infusion pump system with 5% Mannitol fluid bag, e) Olympus (Storz®) 250 Watt halogen light source, and f) hysteroscopic scissors, unipolar electrocautery, and resectoscope for surgical intervention. After the speculum is placed in the dorsolithotomy position on the gynecological table, the vagina is cleaned with povidone iodine solution and the cervix is held with a tenaculum and dilated using Hegar cervical dilators up to number 8-9. The procedure starts with the evaluation of the cervix and cervical canal, and then the internal os is passed and mannitol solution is used to provide 80 mmHg intrauterine pressure for distension of uterine cavity. Both tubal ostia and uterine cavity walls, appearance of endometrium, compatibility with menstrual phase, presence of space-occupying pathology in the cavity and presence of uterine anomaly are evaluated. The structures with or without pedicle that are covered with endometrium and have a smooth surface are defined as polyps. Submucous myomas are defined as vascularized structures protruding into the uterine cavity. Uterine septum is a fibrous tissue that divides the cavity into two and that has various lengths extending from fundus to the internal cervical canal. Regarding intrauterine pathologies detected during HS, the surgeries performed are polypectomy for endometrial polyps, myomectomy for submucous myomas, septum resection in patients with uterine septum and adhesiolysis in patients with adhesion. According to the procedure performed during HS, patients included in the study were divided into two main groups as diagnostic and operative HS. Patients with normal uterine cavity in exploration, who did not require surgical intervention and who did not undergo any additional procedure were referred to as diagnostic HS group, and patients who underwent surgical intervention during the procedure were referred to as operative HS group. Operative HS group was divided into subgroups as endometrial polyp, submucous myoma, septum, adhesion and T-shaped uterus. The data regarding the treatment methods used for pregnancy after HS, whether pregnancy could be achieved and pregnancy outcomes were recorded. Clinical pregnancy, live birth and abortion rates after HS were compared between the groups. Clinical pregnancy was defined as detection of intrauterine embryo heartbeats by US. Abortion was defined as fetal loss of less than 500 grams and/or until 22nd gestational week.

Statistical Analysis

STATA14 (Stata Corp LP, TX, USA) program was used for statistical analysis of the study. The inpopulation distributions of demographic and clinical data of the patients included in the study were evaluated by Shapiro-Wilk test. In the study, Independent Samples t-test Mann-Whitney U test were used to compare the demographic and clinical characteristics of the main groups of operative and diagnostic HS. Chi-square test

was used to compare the reproductive results between the two groups. Mann-Whitney U test was used for the evaluation of laboratory parameters, as they were non-normally distributed. One-way ANOVA and Kruskal Wallis test were used for the evaluation of demographic and clinical parameters among operative HS subgroups, and Kruskal Wallis test was used for the comparison of laboratory parameters. P<0.05 was considered statistically significant at 95% confidence interval, and numerical data were expressed as mean and standard deviation.

RESULTS

Of the 319 patients included in the study, 74 (23.2%) underwent diagnostic HS and 245 (76.8%) underwent operative HS. The results of HS applied to the patients are shown in Table 1. Patients were divided into two groups as diagnostic HS and operative HS. Demographic and clinical characteristics of both groups are shown in Table 2. There was no statistically significant difference between two groups in terms of age, height, weight, BMI and duration of infertility (p>0.05). When the laboratory parameters of the patients who underwent operative and diagnostic HS were examined, no significant difference was found between the two groups in terms of FSH, LH, estradiol, prolactin, TSH and AMH levels (Table 3). While the clinical pregnancy, birth and abortion rates of 213 out of 245 patients who underwent operative HS could be obtained; reproductive results were obtained in 67 of 74 patients who underwent diagnostic HS. The clinical pregnancy, live birth and abortion rates of the operative and diagnostic HS groups were calculated and shown in Table 4. There was no statistically significant difference between the two groups in terms of these parameters (p>0.05). There was no statistically significant difference between the two groups in terms of contraception methods [(in vitro fertilization (IVF), insemination and spontaneous pregnancy] (p=0.260 for diagnostic group and p=0.968 for operative group). The mean time to pregnancy after HS was 9.54 (±9.6) months for the patients in the diagnostic HS group, and 9.96 (±10) months for the patients in the operative HS group. There was no significant difference between the two groups in terms of time to pregnancy after HS (p=0.837). Operative HS patients were divided into polyp, myoma, uterine septum, uterine adhesion and T-shaped uterine subgroups according to HS findings. There was no significant difference between the groups in terms of age, height, weight, BMI and duration of infertility (p=0.585, 0.391, 0.292, 0.544 and 0.971, respectively). Similarly, no statistically significant difference was found between operative HS subgroups in terms of FSH, LH, estradiol, prolactin, TSH and AMH levels (p>0.05). In addition, when the fertility results were evaluated according to the subgroups, the highest clinical pregnancy and live birth rates were seen in the patient group who underwent endometrial polyp and uterine septum resection. The abortion rate was

Table 1. Hysteroscopy findings

Findings	n (%)
Endometrial polyp	146 (45.7%)
Uterine septum	49 (15.4%)
Uterine adhesion	28 (8.8%)
Submucous myoma	12 (3.8%)
T-shaped uterus	10 (3.1%)
Normal uterine cavity	74 (23.2%)

Table 2. Demographic and clinical characteristics of operative and diagnostic hysteroscopy groups

	Operative hysteroscopy (n=245)	Diagnostic hysteroscopy (n=74)	p
Age (years)	32.43±0.32	32.2±0.55	0.549[a]
Height (cm)	161.02±2.35	159.68±1.17	0.114[b]
Weight (kg)	68.73±1.26	67.21±1.96	0.523[b]
BMI (kg/m^2)	26.22±0.44	26.3±0.71	0.878[b]
Infertility period (ay)	53.10±3.53	54.86±5.60	0.641[a]

[a] Mann-Whitney U test; [b]independent-samples t-test, BMI: Body mass index

Table 3. Laboratory parameters of operative and diagnostic hysteroscopy groups

	Operative hysteroscopy (n=245)	Diagnostic hysteroscopy (n=74)	p*
FSH (mIU/mL)	7.39±0.30	7.26±0.50	0.659
LH (mIU/mL)	5.75±0.27	6.07±0.51	0.532
Estradiol (mIU/mL)	52.56±3.73	62.37±9.49	0.731
Prolactin (ng/mL)	15.89±0.67	19.22±2.22	0.539
TSH (µg/mL)	2.35±0.19	1.84±0.20	0.115
AMH (ng/mL)	3.07±0.33	2.88±0.57	0.542

AMH: Anti-mullerian hormone, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone, *Mann-Whitney U test was used for statistical analysis

Table 4. Reproductive outcomes of operative and diagnostic hysteroscopy groups

	Diagnostic hysteroscopy (n=67) n (%)	Operative hysteroscopy (n=213) n (%)	p*
Clinical pregnancy	37 (55.22%)	115 (53.99%)	0.860
Live birth	28 (41.7%)	88 (41.3%)	0.945
Abortion	4 (5.9%)	16 (7.5%)	0.669

*Chi-square test was used for statistical analysis

found to be highest in the patient group with T-shaped uterus (Table 5). In addition to these findings, patients included in the study were evaluated for complications. Uterine perforation was observed in one patient during HS and one patient developed endometritis after the procedure. Both complications were seen in the operative HS group.

Table 5. Reproductive results of operative hysteroscopy subgroups

	Clinical pregnancy rate (%)	Live birth rate (%)	Abortion rate (%)
Endometrial polyp	69/130 (53%)	58/130 (44.6%)	6/130 (4.6%)
Submucosal myoma	4/10 (40%)	3/10 (30%)	1/10 (10%)
Uterine septum	28/43 (65.1%)	18/43 (41.8%)	6/43 (13.9%)
Uterine adhesion	11/24 (45.8%)	8/24 (33.3%)	1/24 (4.1%)
T-shaped uterus	3/6 (50%)	1/6 (16.6%)	2/6 (33.3%)

DISCUSSION

According to the results of our study, there is no significant difference between the operative and diagnostic HS groups and the operative HS subgroups in terms of clinical pregnancy and live birth rates, which are described as reproductive outcomes. Routine use of HS is controversial if no intrauterine pathology is suspected in infertile patients. European Society for Human Reproduction and Embryology and the Royal College of Obstetricians and Gynaecologists do not recommend HS in initial evaluation in patients without indication (6,7). In the National Institute for Health and Care Excellence guideline, HS is not recommended if there is no clinical indication in the initial investigation and treatment of fertility, i.e. if there is no suspicion of uterine anomaly or intrauterine pathology detected by imaging methods such as US, HSG, SIS, since HS does not improve reproductive outcomes when no uterine pathology is detected (8). In a multicenter randomized controlled Trial of Preventing Hypertension study, 702 patients under 38 years of age with recurrent IVF failure and normal uterine cavity were evaluated. Live birth rates between groups with and without performed HS were compared and it was shown that HS before IVF did not increase the live birth rate (9). Similarly, in the Intervention Nurses Start Infants Growing on Healthy Trajectories study, it was reported that routine HS before the first IVF treatment did not change the clinical pregnancy and live birth rates (10). In contrast to these studies, in a randomized prospective study by Rama Raju et al. (11), it reported that the rate of clinical pregnancy and live birth were significantly higher in patients who underwent HS among 520 infertile patients with recurrent IVF failure and normal HSG findings. In the literature, the effect of operative HS on clinical pregnancy acquisition and live birth rates in patients with intracavitary pathology detected by US, HSG and SIS is still unclear. When the operative and diagnostic HS group was compared in patients with uterine cavity pathology, Di Spiezio Sardo et al. (12) did not obtain sufficient evidence showing that clinical pregnancy rates increased. Varasteh et al. (13) evaluated 78 infertile patients who underwent HS, and found that 19 patients had normal cavities, 23 had polyps, and 36 had submucous myomas. It was reported that clinical pregnancy and live birth rates were 42.1% (n=8) and 36.8% (n=7) in the diagnostic HS group, 78.3% (n=18) and 65.2% (n=15) in the polypectomy group, and 52.8% (n=19) and 36.1% (n=13) in the myomectomy group. While clinical pregnancy and live birth rates were found to be significantly different between diagnostic HS and polypectomy groups, no difference was found between diagnostic HS and myomectomy groups. In their study with 215 infertile cases with polyps, Perez-Mediha et al. (14) found that clinical pregnancy rate was 63% and 28% in patients who underwent polypectomy before and without insemination, respectively. In our study, the clinical pregnancy rate was 55.2% and live birth rate was 41.7% in patients without intrauterine pathology in the diagnostic HS group. In the operative HS group, these rates were 53.9% and 41.3%, respectively. In addition, clinical pregnancy rate was 53% and live birth rate was 44.6% in 130 patients who underwent polypectomy. In other words, contrary to the findings of Varasteh et al., (13) there was no statistically significant difference between the diagnostic HS group and the polypectomy subgroup. Another result from the subgroup analysis of the operative HS group was that there was no difference between the diagnostic HS group and the patient group undergoing myomectomy in terms of clinical pregnancy and live birth rates. In our study, the clinical pregnancy rate was 40% and the live birth rate was 30% in the myomectomy group. Ahdad-Yata et al. (15) reported a 33.8% pregnancy rate after hysteroscopic myomectomy, which is similar to our study. However, contrary to our study, Pritts et al. (16) and Shokeir (17) reported increased clinical pregnancy rates with myomectomy. Intrauterine adhesions may prevent sperm migration from the cervical canal or uterine cavity and implantation of the embryo by causing full or partial tubal occlusion. They may cause implantation failure by severe endometrial damage (18). Bhandari et al. (19) found that pregnancy rate after hysteroscopic adhesiolysis was 52.2% and live birth rate was 43.4%. Zikopoulos et al. (20) reported the cumulative live birth rate as 64.7% after the operation. Roy et al. (21) reported that the pregnancy rate after hysteroscopic adhesiolysis was 40.4% and 86.1% of these

cases resulted in live birth. In our study, the clinical pregnancy rate in patients with adhesiolysis was 45.8% and was consistent with the literature. However, in our study, no difference was found in the clinical pregnancy rate between the diagnostic HS group and the adhesiolysis group. Uterine septum is the most common mullerian anomaly seen in 35% of women in the reproductive period (22). Poor blood supply to the septum and cervical insufficiency lead to impaired implantation and poor embryo development (23). In a study by Bendifallah et al. (24), the pregnancy rate after septum resection was 60.9% and the live birth rate was 54.7%. In a review by Nouri et al. (25) which included 18 trials, the clinical pregnancy rate was 60% and the live birth rate was 45% according to the reproductive results of 1501 women. In our study, the rate of clinical pregnancy after septum resection was 65.1% and the live birth rate was 41.8%.

CONCLUSION

As a result, it was concluded that the rate of clinical pregnancy was similar between the patients with corrected intracavitary pathology in the operative HS group and the patients with no evidence of intracavitary pathology in the diagnostic HS group. The results show that hysteroscopic correction of intracavitary pathology increases the rate of clinical pregnancy equivalent to the patients with normal cavity.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of İstanbul University Cerrahpaşa Faculty of Medicine (approval number: 135378).

Informed Consent: Retrospective study.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.E., K.P.B.Ö., Concept: Ş.E., K.P.B.Ö., Design: N.S., K.P.B.Ö., Data Collection or Processing: N.S., Ş.E., Analysis or Interpretation: B.D.Ç., K.P.B.Ö., Literature Search: B.D.Ç., Ş.E., Writing: B.D.Ç., Ş.E.,

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REFERENCES

1. Practice Committee of American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril 2013;99:63.
2. Thoma ME, McLain AC, Louis JF, King RB, Trumble AC, Sundaram R, et al. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. Fertil Steril 2013;99:1324-31.e1.
3. Fritz MA. Female infertility. Speroff L, Fritz MA. Clinical Gynecologic Endocrinology and Infertility. 8th edition. Lippincott Williams & Wilkins; 2010.
4. Féghali J, Bakar J, Mayenga JM, Ségard L, Hamou J, Driguez P, et al. Systematic hysteroscopy prior to in vitro fertilization. Gynecol Obstet Fertil 2003;31:127-31.
5. Kılınç H, Cengiz H, Kaya C, Ekin M, Yaşar L. Endometrial Patolojilerin Değerlendirilmesinde Transvajinal Ultrasonografi ile Ofis Histeroskopinin Karşılaştırılması. Yeni Tıp Dergisi 2012;29:23-6.
6. Crosignani PG, Rubin BL. Optimal use of infertility diagnostic tests and treatments. The ESHRE Capri Workshop Group. Hum Reprod 2000;15:723-32.
7. National Institute for Clinical Excellence. Fertility: Assessment and Treatment for People with Fertility Problems. Clinical guideline 2004;11:23.
8. National Institute for Health and Care Excellence. (2013) Fertility problems: assessment and treatment.Clinical guideline 2013. The web site: http//www.nice.org.uk/guidance/cg156.
9. El-Toukhy T, Campo R, Khalaf Y, Tabanelli C, Gianaroli L, Gordts SS, et al. Hysteroscopy in recurrent in-vitro fertilisation failure (TROPHY): a multicentre, randomised controlled trial. Lancet 2016 25;2614-21.
10. Smit JG, Kasius JC, Eijkemans MJC, Koks CAM, van Golde R, Nap AW, et al. Hysteroscopy before in-vitro fertilisation (inSIGHT): a multicentre, randomised controlled trial. Lancet 201625;387:2622-29.
11. Rama Raju GA, Shashi Kumari G, Krishna KM, Prakash GJ, Madan K. Assessment of uterine cavity by hysteroscopy in assisted reproduction programme and its influence on pregnancy outcome. Arch Gynecol Obstet 2006;274:160-4.
12. Di Spiezio Sardo A, Di Carlo C, Minozzi S, Spinelli M, Pistotti V, Alviggi C, et al. Efficacy of hysteroscopy in improving reproductive outcomes of infertile couples: a systematic review and meta-analysis. Hum Reprod Update 2016;22:479-96.
13. Varasteh NN, Neuwirth RS, Levin B, Keltz MD. Pregnancy rates after hysteroscopic polypectomy and myomectomy in infertile women. Obstet Gynecol 1999;94:168-71.
14. Pérez-Medina T, Bajo-Arenas J, Salazar F, Redondo T, Sanfrutos L, Alvarez P, et al. Endometrial polyps and their implication in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study. Hum Reprod 2005;20:1632-5.
15. Ahdad-Yata N, Fernandez H, Nazac A, Lesavre M, Pourcelot AG, Capmas P. Fertility after hysteroscopic resection of submucosal myoma in infertile women. J Gynecol Obstet Biol Reprod (Paris) 2016;45:563-70.
16. Pritts EA, Parker WH, Olive DL.Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009;91:1215-23.
17. Shokeir TA. Hysteroscopic management in submucous fibroids to improve fertility. Arch Gynecol Obstet 2005;273:50-4.
18. Bosteels J, Weyers S, Puttemans P, Panayotidis C, Van Herendael B, Gomel V, et al. The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review. Hum Reprod Update 2010;16:1-11.
19. Bhandari S, Bhave P, Ganguly I, Baxi A, Agarwal P. Reproductive outcome of patients with Asherman's syndrome: A SAIMS experience. J Reprod Infertil 2015;16:229-35.

20. Zikopoulos KA, Kolibianakis EM, Platteau P, de Munck L, Tournaye H, Devroey P, et al. Live delivery rates in subfertile women with Asherman's syndrome after hysteroscopic adhesiolysis using the resectoscope or the Versapoint system. Reprod Biomed Online 2004;8:720-5.

21. Roy KK, Baruah J, Sharma JB, Kumar S, Kachawa G, Singh N.Reproductive outcome following hysteroscopic adhesiolysis in patients with infertility due to Asherman's syndrome. Arch Gynecol Obstet 2010;281:355-61.

22. Grimbizis GF, Camus M, Tarlatzis BC, Bontis JN, Devroey P. Clinical implications of uterine malformations and hysteroscopic treatment results. Hum Reprod Update 2001;7:161-74.

23. Fedele L, Bianchi S, Marchini M, Franchi D, Tozzi L, Dorta M. Ultrastructural aspects of endometrium in infertile women with septate uterus. Fertil Steril 1996;65:750-2.

24. Bendifallah S, Faivre E, Legendre G, Deffieux X, Fernandez H. Metroplasty for AFS Class V and VI septate uterus in patients with infertility or miscarriage: reproductive outcomes study. J Minim Invasive Gynecol 2013;20:178-84.

25. Nouri K, Ott J, Huber JC, Fischer EM, Stögbauer L, Tempfer CB.Reproductive outcome after hysteroscopic septoplasty in patients with septate uterus-a retrospective cohort study and systematic review of the literature. Reprod Biol Endocrinol 2010;21:8:52.

ORIGINAL ARTICLE

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Idiopathic Scrotal Calcinosis: A Review of the Literature with Seven Cases

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Abstract

Objective: Scrotal calcinosis is a rare benign disease characterized by calcified nodules on the scrotum skin. In this article, seven patients who were diagnosed as idiopathic scrotal calcinosis were reviewed with the relevant literature.

Methods: Seven patients who were operated for scrotal calcinosis between 2007 and 2015 were included in the study. Patients' age, admission symptoms, accompanying symptoms, duration of symptoms, size and number of masses, type of anesthesia, type of treatment, duration of hospitalization, complications and disease recurrence were evaluated.

Results: All patients presented with a painless mass in the scrotum and their ages ranged from 18 to 67 years (mean 34.2 years). The mean time from the onset of the disease to the time of admission was 2.5 years (range, 6 months-9 years). The masses ranged from 2 mm to 40 mm. There were no pathological findings in the systemic examinations except the lesions in the scrotum. One patient was operated under local anesthesia, three patients under spinal anesthesia and three patients under general anesthesia. The patients were removed from follow up at their own request after 12 months. No recurrence was observed during the follow up period.

Conclusion: Although there are various theories about the etiology of the disease, its etiology is still controversial and the disease is considered idiopathic.

Keywords: Etiology, calcinosis, scrotum

INTRODUCTION

Idiopathic scrotal calcinosis is a very rare benign skin disease characterized by numerous asymptomatic calcified nodules on the scrotum skin (1,2). Although it was described by Lewinski (3,4) in 1883, it was long after Shapiro et al. (5) and his colleagues proposed the name "idiopathic scrotal calcinosis". The disease starts in the third decade. Although it is frequently seen in young adults, it can also be seen in other age groups, and the number and size of nodules tend to increase over time. The masses are dirty yellow and can reach sizes ranging from 1 mm to 3-4 cm. The largest reported nodule size is around 7 cm (6). Although the lesions are mostly painless and cause cosmetic problems, it may rarely present with pruritus, secondary infection and a chees-like drainage. The calcium and phosphorus deposits on the scrotum skin are microscopically observed as amorphous basophilic masses and the lesions are usually accompanied by foreign body reaction (3,7). In the biochemical analysis of nodules, phosphate, carbonate, magnesium and calcium are found (2). The etiology of the disease is not clear. Although it is accepted as idiopathic, some metabolic (metastatic calcification, hyperparathyroidism, sarcoidosis) and systemic diseases (dermatomyositis, scleroderma) have been implicated in the etiology (8). Clinically, scrotal calcinosis can be confused with other benign masses such as epidermal inclusion cyst, cutaneous horn, lipoma, fibroma, angiokeratoma and lymphangioma circumscriptum (9). The definitive diagnosis is made by histopathological examination after excision of the masses. The treatment of the disease is surgical and cure is provided. In this article, seven patients who were diagnosed as idiopathic scrotal calcinosis were reviewed with the relevant literature.

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METHODS

Seven patients aged between 18 and 67 years (mean 34.2 years), who underwent surgery for scrotal calcinosis between 2007 and 2015, were included in the study. Patients' age, admission symptoms, accompanying symptoms, duration of symptoms, size and number of masses, type of anesthesia, type of treatment, duration of hospitalization, complications and disease recurrence were evaluated.

RESULTS

All of the patients presented with a painless mass in the scrotum, and one patient had pruritus before the admission (Table 1). The mean time from the onset of the masses to the time of admission was 2.5 years (range, 6 months to 9 years). It was learned that the numbers and sizes of masses gradually increased over time, appearing as raised, yellow colored masses. At the time of admission, one patient had a single mass, and six patients had multiple masses (Figures 1, 2). The masses ranged from 2 mm to 40 mm. On examination, it was observed that well circumscribed hard masses were not tender. None of the patients had scrotal trauma, systemic disease, metabolic disease and positive family history. Systemic examination of the patients was normal except for these lesions in the scrotum. No pathology was detected in laboratory tests. One patient was operated under local anesthesia, three patients under spinal anesthesia and three patients under general anesthesia. Spinal and general anesthesia preferences were determined according to the extensity of the lesions and the preference of the patients. The masses were excised with intact skin margin and all defects were closed using simple sutures (Figure 3). The patient who was operated with local anesthesia was discharged on the same day and the other patients were hospitalized for one day and discharged with oral antibiotics and analgesics. None of the patients had any early or late complications. Histopathological examination results were reported as idiopathic scrotal calcinosis. The patients were removed from follow up at their own request after 12 months. No recurrence was observed during the follow up period (Figure 4).

DISCUSSION

Idiopathic scrotal calcinosis is a rare disease presenting with numerous asymptomatic nodules on the skin of the scrotum (1,7). Nearly 200 cases have been reported since its description at the end of the 19th century. Although it is frequently seen in children and young adults, it is also seen in other age groups (2,5,7). In the literature, the oldest patient is 85 years old and the youngest patient is 9 years old (10). In our series, the admission age was in the young adult age group with the youngest patient being 18 years old and the oldest patient being 67 years old. The numbers and sizes of the masses tend to increase slowly over time (2,7). Generally, the number is more than one. In our

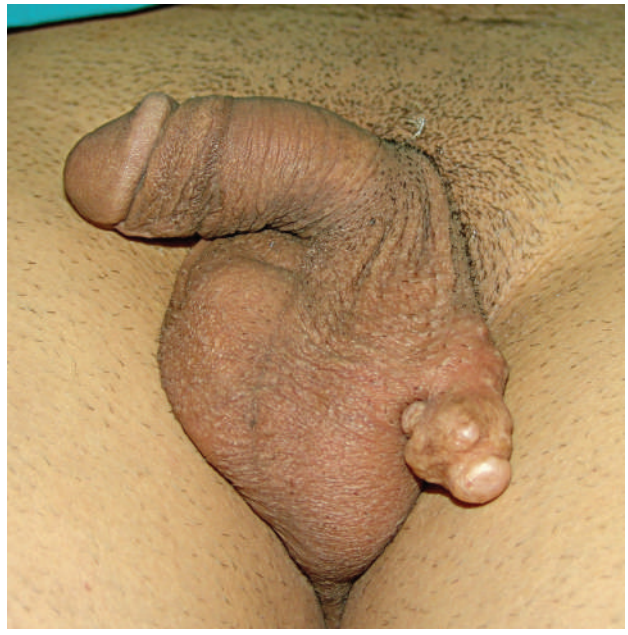

Figure 1. The appearance of single scrotal nodule on the scrotum

Table 1. Demographic data of patients

Patient ID	Age, years	Symptoms	Symptom duration	Mass size and number	Length of hospital stay	Anesthesia type
1	22	Painless mass	1 year	Multiple, 2 mm-5 mm	1 day	Spinal
2	18	Painless mass	6 months	Multiple, 3 mm-25 mm	1 day	Spinal
3	56	Painless mass	3 years	Multiple, 2 mm-30 mm	1 day	Spinal
4	32	Painless mass	2 years	Single, 30 mm	Same-day	Local
5	67	Painless mass, pruritus	9 years	Multiple, 4 mm-30 mm	1 day	General
6	21	Painless mass	2 years	Multiple, 2 mm-3 mm	1 day	General
7	24	Painless mass	9 months	Multiple, 4 mm-40 mm	1 day	General

ID: Identify

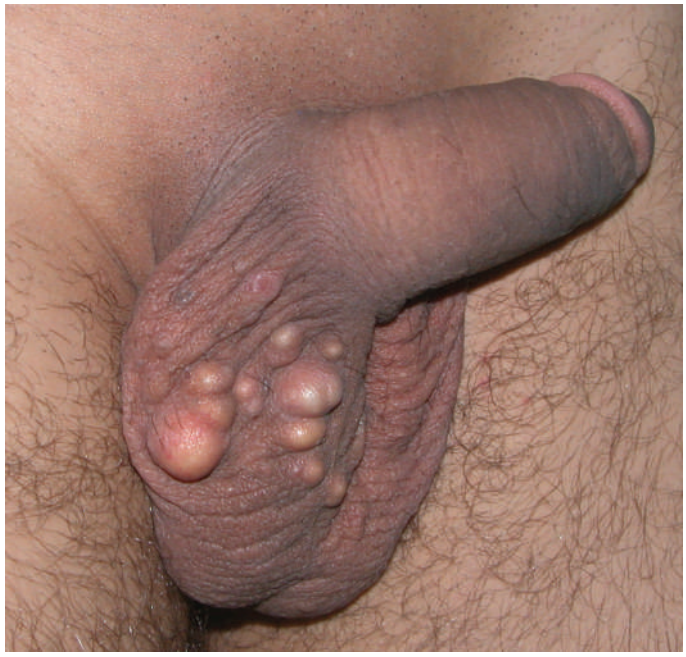

Figure 2. Appearance of various sized nodules on the scrotum skin

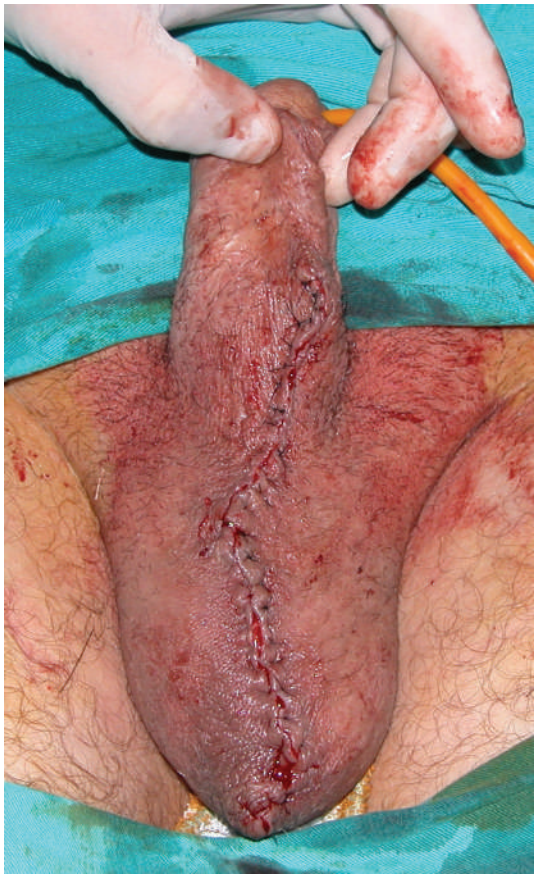

Figure 3. Early postoperative appearance

cases, one patient presented with a single nodule and multiple lesions were detected in six patients. In one patient, pruritus was detected as a concomitant symptom. Generally, they are painless

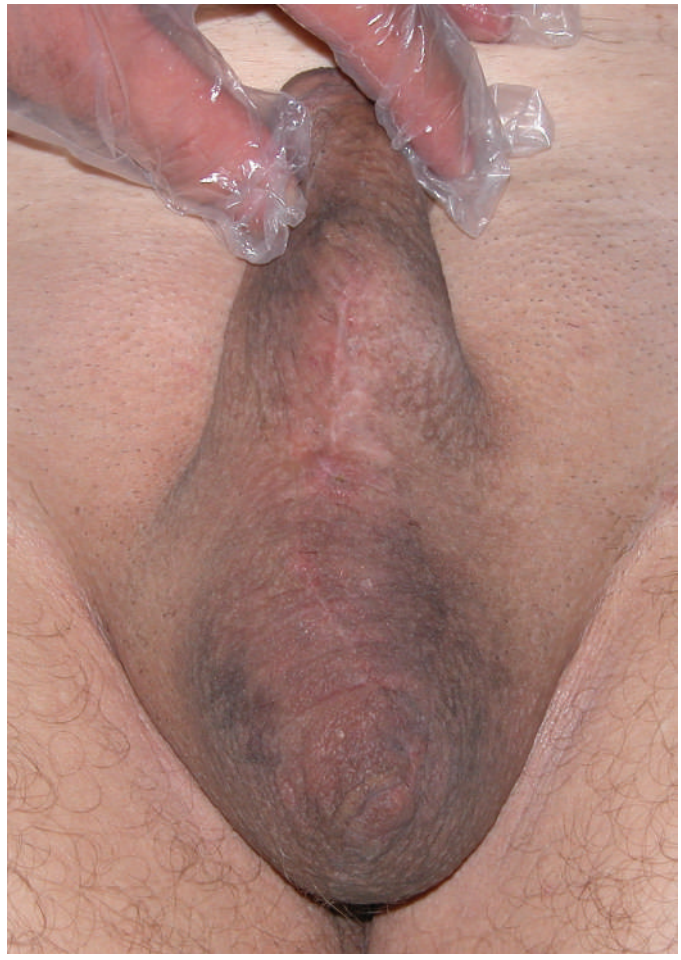

Figure 4. Postoperative 1st year appearance

lesions and they rarely present with itching, signs of secondary infection and drainage of mass content secondary to the trauma (5). The calcium phosphate hydroxyapatite crystals deposited in the scrotum tissue are observed as amorphous basophilic masses in pathological evaluation and the lesion is often accompanied by foreign body reaction (2,7). However, microscopically, it has morphologic variability ranging from epidermal cyst to calcified dermal nodules (2). Although different theories regarding the etiology of scrotal calcinosis have been proposed, the disease is thought to be idiopathic (2,7,11-14). It has been suggested that calcifications are caused by trauma (12) or by calcification of the dartos muscle (13) or dystrophic calcification caused by inflammation of the epidermal cyst (14). Veress and Malik (12) and Feinstein et al. (15) suggested that minor trauma contributed to the development of dystrophic calcification. Ultrastructural studies carried out by Takayama et al. (16) and Pak et al. (17) revealed the presence of calcium and phosphorus mineral crystals. High amounts of calcium, phosphorus, granular crystals and cell residues have been described by Füzesi et al. (18) using electron microscopy and radiographic microanalysis.

Although these findings support the hypothesis that there is a degenerative starting source for scrotal calcinosis, they do not fully explain the mechanism. In the presented cases, no history of trauma was reported. Many researchers have detected foreign body elements in the calcified nodule and fascicles of the dartos muscle (13,19,20). In a histological study, King et al. (13) found calcification foci regularly surrounded by dartos muscle bundles, and necrosis of the dartos muscle was suggested to be a result of the degeneration of the dartos muscle with dystrophic calcification in a process similar to the calcification of uterine leiomyoma (21). One of the unproven hypotheses is that dartos muscle degeneration and necrosis may be an important factor in the pathogenesis of scrotal calcinosis (19). Swinehart and Golitz (14) is the first to suggest that scrotal calcinosis originates from epidermal inclusion cysts and reported cases of scrotal calcinosis developed from epidermal cysts in 1982. They observed the stages of inflammation associated with scrotal calcinosis and calcific keratin and minimal active inflammation in some cysts. As a result of these findings, some researchers have developed the hypothesis that scrotal calcinosis causes calcium precipitation by inflammation of ruptured epithelial cysts (2,14,22,23). The etiology of the disease was accepted as idiopathic in our study since no epithelial cells or signs of degeneration were observed in the microscopic examination of the pathological specimens of the presented patients and no other etiologic factors could be identified. This distinction is not clinically important, as histopathological findings support idiopathic calcinosis and thus it does not make a difference in the etiology and does not change the treatment. As the lesions are limited to the dermis, excision of the scrotum skin is sufficient for treatment. Although there is no consensus on the pathogenesis of scrotal calcinosis, the recommended treatment is surgery. Scrotum skin is usually repaired primarily, but in the presence of very extensive lesions, alternative reconstruction options such as skin grafts and local flaps have been reported (24-27). In all of our cases, defects that were formed after excisions were repaired primarily and cosmetic results after surgery were acceptable. In scrotal calcinosis, surgery is a curative treatment and recurrence is rare (27,28). No recurrence was observed in the 12th month follow up after surgical treatment.

CONCLUSION

As observed in our series, the majority of patients with scrotal calcinosis present to the hospital due to painless masses. There are no sensitive and specific findings in the medical history of the patients and routine laboratory tests. Surgical excision and histopathological examination is necessary to confirm the diagnosis. Although the etiologic factor does not change the treatment plan, we think that the term "idiopathic" is appropriate for these cases.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S., O.A., Concept: M.S., O.A., Design: M.S., O.A., Data Collection or Processing: M.S., O.A., Analysis or Interpretation: M.S., O.A., Literature Search: M.S., O.A., Writing: M.S., O.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Özgenel GY, Kahveci R, Filiz G, Ozcan M. Idiopathic scrotal calcinosis. Ann Plast Surg 2002;48:453-4.
2. Song DH, Lee KH, Kang WH. Idiopathic calcinosis of the scrotum: histopathologic observations of fifty-one nodules. J Am Acad Dermatol 1988;19:1095-101.
3. Saad AG, Zaatari GS. Scrotal calcinosis: is it idiopathic? Urology 2001;57:365.
4. Pompeo A, Molina WR, Pohlman GD, Sehrt D, Kim FJ. Idiopathic scrotal calcinosis: A rare entity and a review of the literature. Can Urol Assoc J 2013;7:E439-41.
5. Shapiro L, Platt N, Torres-Rodriguez VM. Idiopathic calcinosis of the scrotum. Arch Dermatol 1970;102:199-204.
6. Koçak T, Çizmeci O, Mete Ö, Zorba OÜ. Idiopathic scrotal calcinosis presenting as three nodules, one being 7-cm in diameter. Turk J Urology 2009;35:157-8.
7. Karaca M, Taylan G, Akan M, Eker G, Gideroglu K, Gul AE. Idiopathic scrotal calcinosis: surgical treatment and histopathologic evaluation of etiology. Urology 2010;76:1493-5.
8. Michl UH, Gross AJ, Loy V, Dieckmann KP. Idiopathic calcinosis of the scrotum-a specific entity of the scrotal skin. Scand J Urol Nephrol 1994;28:213-7.
9. Lei X, Liu B, Cheng Q, Wu J. Idiopathic scrotal calcinosis: report of two cases and review of literature. Int J Dermatol 2012;51:199-203.
10. Baruchin AM, Baruffaldi Preis FW, Cavallini M, Ben-Dor D. Idiopathic calcinosis of the scrotum: report of five cases and review of the literature. Eur J Plast Surg 1998;21:282-5.
11. Tosun Z, Karaçor Z, Ozkan A, Toy H, Savaci N. Two scrotal calcinosis cases with different causal mechanisms. Plast Reconstr Surg 2005;116:1834-5.
12. Veress B, Malik MO. Idiopathic scrotal calcinosis: A report of six cases from Sudan. East Afr Med J 1975;52:705-10.

13. King DT, Brosman S, Hirose FM, Gillespie LM. Idiopathic calcinosis of scrotum. Urology 1979;14:92-4.
14. Swinehart JM, Golitz LE. Scrotal calcinosis. Dystrophic calcifications of epidermoid cysts. Arch Dermatol 1982;118:985-8.
15. Feinstein A, Kahana M, Schewach-Millet M, Levy A. Idiopathic calcinosis and vitiligo of the scrotum. J Am Acad Dermatol 1984;11:519-20.
16. Takayama H, Pak K, Tomoyoshi T. Electron microscopic study of mineral deposits in idiopathic calcinosis of the scrotum. J Urol 1982;127:915-8.
17. Pak K, Takayama H, Tomoyoshi T. Idiopathic calcinosis of scrotum. Urology 1983;21:521-3.
18. Füzesi L, Hollweg G, Lagrange W, Mittermayer C. Idiopathic calcinosis of the scrotum: scanning electron microscopic study with x-ray microanalysis. Ultrastruct Pathol 1991;15:167-73.
19. Pabuççuoğlu U, Canda MS, Güray M, Kefi A, Canda E. The possible role of dartoic muscle degeneration in the pathogenesis of idiopathic scrotal calcinosis. Br J Dermatol 2003;148:827-9.
20. Fischer BK, Dvoretzki I. Idiopathic calcinosis of the scrotum. Arch Dermatol 1978;114:957-60.
21. Gi N, Gupta AK, Sachi K, Thomas S. Idiopathic scrotal calcinosis – a pedunculated rare variant. J Plast Reconstr Aesthet Surg 2008;61:466-7.
22. Melo CR, Schmitt FC, Melo IS, Vaca J, Lucia Caetano A, Souza F. Calcinosis of the scrotum: report of a case associated with epidermoid cysts. Med Cutan Ibero Lat Am 1988;16:355-8.
23. Sarma DP, Weilbaecher TG. Scrotal calcinosis: calcification of epidermal cysts. J Surg Oncol 1984;27:76-9.
24. Gürdal M, Sayan S, Kılıç G, Karaman Mİ. Skrotal kalsinozis. Türk Üroloji Dergisi 2001;27:368-70.
25. Emir L, Fidan V, Germiyanoğlu C, Erol D. İdiyopatik skrotal kalsinozis: Skrotumun nadir bir hastalığı. Türk Üroloji Dergisi 2003;29:101-3.
26. Theuvenet WJ, Nolthenius-Puylaert T, Giedrojc Juraha ZL, Borghouts JM, van Twisk R. Massive deformation of the scrotal wall by idiopathic calcinosis of the scrotum. Plast Reconstr Surg 1984;74:539-43.
27. 27 Dini M, Colafranceschi M. Should scrotal calcinosis still be termed idiopathic? Am J Dermatopathol 1998;20:399-402.
28. Ruiz-Genao DP, Rios-Buceta L, Herrero L, Fraga J, Aragues M, Garcia-Diez A. Massive scrotal calcinosis. Dermatol Surg 2002;28:745-7.

ORIGINAL ARTICLE

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Prediction of Preeclampsia by Uterine Artery Doppler Examination and Placental Growth Factor, Endoglin and Pregnancy-associated Plasma Protein Levels in Maternal Serum at 11-13+6 Pregnancy Week

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Abstract

Objective: We aimed to evaluate the prediction of preeclampsia by maternal serum pregnancy-associated plasma protein A (PAPP-A), placental growth factor (PIGF), sEndoglin (sEng) and uterine artery Doppler examination.

Methods: One hundred and ninety-three singleton pregnant women admitted to outpatient clinic at 11-13+6 weeks for first trimester combined screening test were included in the study. Maternal history was taken, and uterine artery Doppler examination and serum biomarker screening (PAPP-A, PIGF, sEndoglin) were conducted. The follow-up results of pregnancy were recorded. The study cohort was divided into two groups as "control" and "preeclampsia". Mann-Whitney U and chi-square tests were used for comparison of independent variables. Sensitivity and specificity for the predictive values of the significant parameters were calculated from ROC curves.

Results: Of 193 women, 168 women (87%) were in the control group (group 1) and 25 women (12.9%) who developed preeclampsia were defined in the preeclampsia group. In preeclampsia group, 20 women (10.3%) with gestational hypertension and mild preeclampsia were defined as "group 2", and five women (2.5%) with severe preeclampsia and hemolysis, elevated liver enzymes, low platelet were defined as "group 3". Maternal serum PAPP-A, PIGF, sEng levels were not significantly different between preeclampsia group and control group, whereas uterine artery Doppler pulsatility index (PI) values were significantly higher in preeclampsia group (p=0.023). sEng levels were significantly higher in group 3 than those in group 2 (p=0.001). If uterine artery PI cut-off level was taken as >2.23 in ROC curve analysis, sensitivity was 42.31% and specificity was 82.10% for detecting preeclampsia.

Conclusion: Maternal serum PAPP-A, PIGF and sEng were not effective in predicting preeclampsia. However, these markers can be used to distinguish between mild and severe preeclampsia. First trimester uterine artery Doppler examination is an effective screening method for predicting preeclampsia.

Keywords: Preeclampsia, uterine artery, pregnancy-associated plasma protein A, placental growth factor, sEndoglin

INTRODUCTION

Preeclampsia (PE) affects approximately 2% of all pregnancies and it is the most significant cause of maternal perinatal mortality and morbidity (1). Today, early detection of PE has become one of the fundamental goals of perinatal medicine. Although clinical symptoms of PE emerge after 20th week of gestation, trophoblast invasion that is responsible for pathogenesis occurs in the first trimester (2). High-resistant spiral arteries can be detected from the 11th week of gestation by uterine artery (UtA) Doppler examination (3). Therefore, first trimester UtA Doppler examination may be a good noninvasive method for predicting PE that reflects abnormal trophoblast invasion. The addition of maternal history and biochemical serum markers to UtA Doppler examination is strongly associated with placental and endothelial dysfunction (4). These markers make screening relatively earlier, and most importantly, when used with first

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trimester Doppler sonography, they provide higher predictive value and more advanced diagnostic performance (5). Placental growth factor (PIGF) and vascular endothelial growth factor (VEGF) are potent angiogenic factors and they have a stimulating effect on endothelial cell proliferation and migration. Soluble fms-1ike tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng) are anti-angiogenic factors and it is suggested that hypoxic placenta secretes increased amounts of sFlt-1 and sEng (6,7). Although there are contradictory results in the studies, it has been generally reported that the levels of angiogenic factors, PIGF and VEGF, are decreased in PE and the levels of anti-angiogenic factors, sFlt-1 and sEng, are increased (8). In addition, pregnancy-associated plasma protein A (PAPP-A) and free beta human chorionic gonadotropin (f-ßhCG) have been used for chromosomal abnormality screening tests, and they have been also investigated in the prediction of complications that emerge in advanced gestational weeks in many studies and their availability has been discussed (9). Studies have shown that especially low PAPP-A levels may be closely associated with PE (10). Prediction of PE prediction has an important role in the prevention of complications associated with PE. Based on this reality, we intended to investigate the possible relationship between the development of PE development and maternal serum PIGF, sEng, PAPP-A, f-βhCG levels that were measured at 11+0 and 13+6 weeks of gestation and UtA pulsatility index (PI) values determined by Doppler ultrasonography.

METHODS

Singleton pregnant women who admitted for screening test at 11+0 and 13+6 weeks of gestation were included in the study. The study was planned as a prospective cohort study. Ethics committee approval was taken and cases were informed about the study. Exclusion criteria were determined as pregnancy greater than 14 weeks, multiple pregnancy, chromosomal or congenital fetal abnormality, chronic hypertension, molar pregnancy, type 1 diabetes mellitus, maternal renal disease, PE history and morbid obesity. Detailed maternal history was taken, ad nuchal translucency measurement and UtA Doppler examination were done. When consecutive similar wave patterns were obtained, PI was measured; mean PI values of right and left UtAs were calculated. Doppler measurement of the UtA PI at 11-13+6 weeks was performed by the same experienced sonographer. PAPP-A and f-βhCG were studied from blood samples. Measurements were performed using Immulite 2000 systems autoanalyzer with Siemens kits and by chemiluminescence method. The measurements were converted to multiple of median (MoM) values. Centrifuged blood samples were stored at -80 ˚C to analyze PIGF and sEng levels. After the completion of the study groups, human sEng/CD105 ELISA (Aviscera Biscience, Inc. Santa Clara, USA) and PIGF ELISA (DRG Instruments GmbH, Germany) kits were tested using micro-ELISA method by Radim Aliysei instrument in stored serum samples.

Characteristics, medical history, pregnancy outcomes, sonography findings, systolic and diastolic blood pressure values, pregnancy complications, PIGF, sEng, MoM values of PAPP-A and f-βhCG of the cases were recorded in computer database. PE diagnosis was made when two different blood pressure measurements, measured every 4 hours, were 140/90 mmHg and above, and presence of 300 mg or more protein in the urine within 24 hours or presence of 30 mg/dL (1+dipstick) protein in spot urine sample following 20th weeks of pregnancy. According to ACOG criteria, PE group was divided into two groups as severe (group 3) and mild PE (group 2) (11). In case of only high blood pressure, gestational hypertension (GHT) was diagnosed; and in case of additional hemolysis, increase in liver enzymes and thrombocytopenia to PE-eclampsia table, hemolysis, elevated liver enzymes, low platelet (HELLP) was diagnosed (12). Group 1 was composed of pregnant women who did not develop complications and group 2 was composed of patients with the diagnosis of PE, GHT and HELLP.

Statistical Analysis

SPSS (Statistical Package of Social Sciences) 16 evaluation version was used in the analysis of collected data. Mann-Whitney U test was used for statistical assessment and chi-square test was used for the comparison of classifier data. The differences between mild PE, severe PE and control group in terms of independent variables were analyzed by Kruskal Wallis test. The correlations between the variables were determined by Spearman correlation analysis. Results were evaluated at 95% confidence interval and significance was evaluated at $p<0.05$ level.

RESULTS

The study was performed on 250 pregnant women between 16-41 years of age who admitted to Kocaeli University Faculty of Medicine, Department of Obstetrics and Gynecology between February 2012 and 2014. Fifty-seven cases from whom we could not get pregnancy outcomes were excluded from the study. Out of patient group including 193 cases with serum PAPP-A, f-βhCG, PIGF and sEng measurements performed in 11-14 weeks of gestation and with known pregnancy outcomes, 168 women were not affected by PE, whereas PE was detected in 25 women including severe PE in 4 cases, mild PE in 18 cases, GHT in 2 cases and HELLP in one case. Patients with uncomplicated pregnancy

were classified as group 1 (n=168), and patients diagnosed with mild PE, severe PE, GHT and HELLP were classified as group 2 (n=25). None of the pregnant women included in the study had a history of smoking or pregnancy with assisted reproductive techniques in vitro fertilization. Demographic characteristics and pregnancy outcomes of the patients are given in Table 1. When preeclamptic and normotensive patients were compared based on maternal age, gravida, parity, body mass index, delivery week and values, no statistically significant difference was found (p>0.05) (Table 1). There was a significant difference in terms of birth weight of the newborn, mean arterial systolic pressure and mean diastolic pressure (p<0.05). There was no statistically significant difference between preeclamptic and control groups in terms of PIGF, sEng, PAPP-A, f-βhCG serum markers. UtA PI (p=0.023) and systolic diastolic (p=0.019) ratio were significantly higher in the preeclamptic group. The groups are shown in Table 1.When we classified cases as control group (n=168), patients who developed mild PE and GHT (n=20) (group 2), and patients who developed severe PE and HELLP (n=5) (group 3), sEng level in group 3 was significantly higher than in group 2 (Table 2). PIGF level was relatively decreased in group 3 compared to group 2, however it was not statistically significant. PAPP-A MoM value was found to be significantly lower in group 3 compared to group 2. These results are summarized in Table 2. Prediction of PE could be made by ROC analysis with a PI cut-off value of >2.23, with a sensitivity of 42.31% and a specificity of 82.10%. It is summarized in Table 3 and Figure 1.

Table 1. Demographic characteristics, serum biochemistry and ultrasonography results of the patients

Characteristics	Group 1 (control) (n=168)	Group 2 (preeclamptic) (n=25)	p
Maternal age (years)	28.5±5.90	30.03±6.39	0.494
Gravida	1.97±1.16	2.10±1.03	0.553
Parity	1.2±0.9	1.5±1.4	0.600
Body mass index (kg/m^2)	28.3±3.3	29.3±6.7	0.59
Delivery week	38.06±2.88	38.40±1.81	0.537
Weight of newborn (gr)	3080±53.51	2615±189.87	0.03
Mean systolic blood pressure	111.15±18.14	148.21±19.53	<0.0001
Mean diastolic blood pressure	70.54±9.45	98.05±13.18	<0.0001
PIGF (pg/mL)	71.25±0.9	67.24±1.1	0.571
sEndoglin (ng/mL)	15.38±0.2	15.82±0.3	0.642
PAPP-A (MoM)	1.2	1.01	0.417
f-βhCG (MoM)	1.2	0.91	0.184
UtA-PI	1.67±0.35	1.93±0.23	0.023
UtA-S/D	3.76±0.2	4.85±0.1	0.019

Values are mean ± standard deviation or n (%)
PIGF: Placental growth factor, PAPP-A: Pregnancy associated plasma protein-A, f-βhCG: Free chorionic gonadotropin, UtA-PI: Uterine artery pulsatility index measurement, UtA-S/D: Uterine artery systolic diastolic ratio, MoM: Multiple of median

DISCUSSION

Prediction of PE in the first trimester, where maximum trophoblastic invasion occurs before the onset of the disease, is definitely an important goal. Therefore, many biochemical markers that can provide an estimate of PE are still being investigated. An ideal test should be simple, rapid, cost effective and easy to use. Positive likelihood ratio should be >15 and negative likelihood ratio should be <0.1. Its sensitivity and specificity should also be high. Today, there are no tests that are sufficient for PE prediction alone or in combination. While screening test which uses maternal obstetric history is quite

Table 3. Uterine artery pulsatility index cut-off value in preeclampsia prediction

	Cut-off PI	AUC %95 (CI)	LR+/ LR-	Specificity	Sensitivity
Preeclampsia	>2.23	0.639 (0.566 -0.708)	2.36/0.7	82.10%	42.31%

PI: Pulsatility index, AUC: Area under curve, CI: Confidence interval, LR: Likelihood ratio

Table 2. Comparison of serum markers and uterine artery pulsatility indexes between mild preeclampsia, severe preeclampsia and control groups

Median (25-75 p)	Group 2 (n=168)	Group 2 (n=20)	Group 3 (n=5)	p
PIGF (pg/mL)	71.25 (48.08-134.58)	76.05 (41.41-134.9)	66.1 (34.39-76.68)	0.24
sEndoglin (pg/mL)	1538 (1319-1732)	1497 (1232.75-1671.75)	1915 (1804-2212.5)	**0.001**
PAPP-A MoM	1.2 (0.81-1.72)	1.18 (0.71-1.93)	0.55 (0.45-0.86)	**0.029**
f-βhCG MoM	1.02 (0.69-1.51)	0.93 0.55-1.33)	0.74 (0.52-1)	0.15
UtA-PI	1.67 (1.34-2.07)	1.84 (1.5-2.55)	2.07 (1.86-2.71)	**0.023**

PIGF: Placental growth factor, PAPP-A: Pregnancy associated plasma protein-A, f-βhCG: Free chorionic gonadotropin, UtA-PI: Uterine artery pulsatility index measurement, MoM: Multiple of median

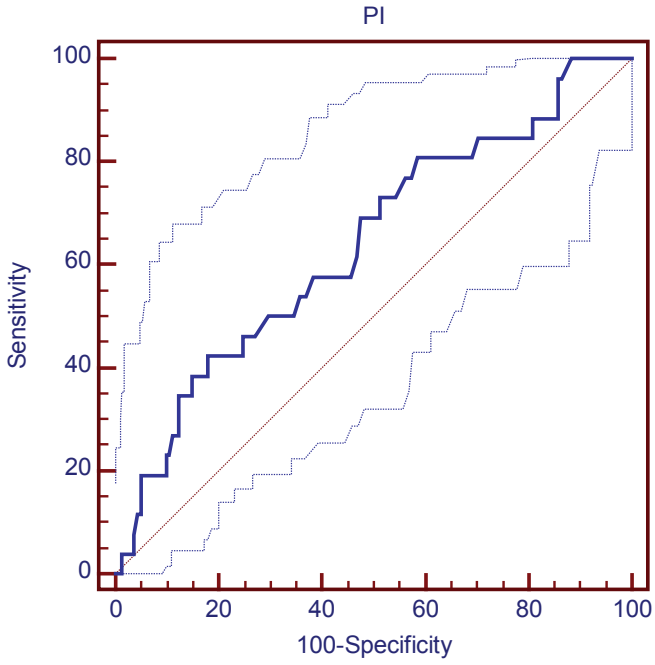

Figure 1. ROC curve analysis of uterine artery Doppler pulsatility index for prediction of preeclampsia
PI: Pulsatility index

insufficient, Harrington et al. (13) proved that PE screening might be possible by bilateral UtA Doppler examination with a high sensitivity and low specificity in the mid-1900s. In a large prospective study, the relationship between UtA Doppler findings [resistance index (RI) and diastolic notch] and the development of term and preterm PE at 11 and 14 weeks of gestation was investigated, and 57 term and 33 early PE cases were detected among 3058 pregnant women. The sensitivity of UtA Doppler examination in the detection of PE was found to be 49% within 90 percentile. In addition, it was indicated that when RI of UtA Doppler was greater than 90 percentile, there was a 6-fold increase in the likelihood of early PE. The mean RI values of early preeclamptic women were higher compared to preeclamptic women at term (14). In a retrospective study, first and second trimester UtA Doppler indices of 3560 pregnant women were investigated within a 7-year period and PE was detected in 126 pregnant women. It was determined by ROC analysis that PI value was the best predictor of PE. The difference between mean second trimester and first trimester PI values was found to be 0.851 in PE prediction before 34 gestational weeks and 0.786 for late PE, and the authors stated that the difference between two trimester mean PI values could be used in the prediction of PE (15). In our study, when UtA PI cut-off value was taken as >2.23 in the prediction of PE cases, sensitivity was 42.31% and specificity was 82.10%. In recent years, new screening protocols have been introduced to the literature by Fetal Medicine Foundation with the combined evaluation of maternal characteristics, UtA Doppler and angiogenic-antiangiogenic markers (16). The addition of maternal history and biochemical serum markers to UtA Doppler examination was strongly associated with placental and endothelial dysfunction (4,5). Serum PIGF, sEng, sFlt-1 and placental protein 13 (PP-13) make it possible to make screening earlier, and most importantly, when used with first trimester Doppler sonography, they provide a higher predictive value and more advanced diagnostic performance (5). While PAPP-A alone provides a prediction of 10-20% during PE screening, it can provide a prediction of 70% [5% false positivity rate (FPR)] when combined with UtA Doppler indices (10,17). Spencer et al. (18) performed PAPP-A and PP-13 measurements in the first trimester and UtA Doppler examinations at 22-24 weeks of gestation. PAPP-A MoM value was found to be significantly lower in preeclamptic group compared to the control group. When PAPP-A was combined with UtA PI value, PE could be estimated with 76% sensitivity; however, there was no change in sensitivity with the addition of PP-13 to this combination. In their study, Di Lorenzo et al. (19) detected a significant relationship between early-onset PE and f-βhCG value above 3.0 MoM. However, many studies retrospectively evaluating f-βhCG have shown that it is unable to predict PE (10,20). In a study evaluating sEng level at 11-13 and 30-33 weeks of gestation, the median MoM value at 30-33 weeks of gestation was found to be higher in preeclamptic group compared to control group, and sEng level at 11-13 weeks of gestation was found to be similar between the two groups. When maternal characteristics were combined with third trimester sEng levels, late-onset PE prediction was reported as 50% with a FPR of 10% (21). PIGF is a proangiogenic protein and PE has been associated with the production of smaller amounts of this protein. Decrease in concentration may occur during clinical symptoms and preclinical period of the disease, and it is present since first trimester. In the first trimester, preeclamptic pregnant women were found to have low PIGF concentration and it was inversely proportional to the severity of the disease (22). No difference was found between normotensive and preeclamptic patients in terms of PIGF levels tested in urine at 8-21 weeks of pregnancy. Regarding PE prediction, preterm PIGF level in the 21-32 weeks of pregnancy was higher compared to term PIGF level (23). Akolekar et al. (24) examined UtA PI, mean blood pressure, PIGF, PAPP-A values in 58.884 cases at 11-13 weeks of pregnancy. They reported a PE detection rate of 50% with a FPR of 10% by using only maternal body mass index (BMI) and mean artery pressure at 34 weeks of pregnancy and a detection rate of 75% with the addition of UtA PI and more than 95% with the addition of PIGF and PAPP-A values (24). However, Diguisto et

al. (25) reported that the multivariate model adjusted according to laboratory and sonographic indicators had an area under the curve (AUC) estimated at 0.76, which was not significantly different from the AUC of the univariate model adjusted only for PlGF (p=0.7). As a result, in a high-risk population, PlGF in the first trimester is useful for predicting PE, but neither sFlt-1 nor any UtA Doppler indices improved the prediction of PE (25). Li et al. (26) demonstrated that UtA PI at early second-trimester was increased in pregnancies that developed PE (1.61±0.047 vs. 1.02±0.049, p<0.001). In contrast, the level of PlGF was decreased in preeclamptic group compared to controls (0.69±0.23 vs. 1.00±0.26, p<0.001) (26).

UtA PI, PAPP-A, PIGF, PP-13, inhibin-A, activin-A, sEng and mean arterial pressure were studied in 33, 602 pregnant women at 11-13 weeks of pregnancy. When only maternal factors (history), UtA PI, blood pressure and PAPP-A were evaluated in PE cases, early PE was estimated by 33% with a FPR of 5%, PE between 34-37 weeks was estimated by 27.8% and PE after 37 weeks was estimated by 24.5%. PE prediction rate was reported as 91%, 79.4% and 60.9%, respectively, with the addition of other biochemical markers to maternal factors (4). In combined screening with maternal factors, mean arterial pressure, UtA PI and PLGF detection rate was 100% [95% confidence interval (CI) 80-100] for PE at <32 weeks, 75% (95% CI 62-85) for PE at <37 weeks and 43% (95% CI 35-50) for PE at ≥37 weeks, at 10% FPR. The combination of maternal factors and biomarkers provides effective first trimester screening for preterm PE (27). Poon et al. (28) investigated 7797 singleton pregnant women at 11-13 weeks of pregnancy. The authors predicted that early-onset PE would develop in 476 patients by logistic regression analysis using variables of UtA PI, mean blood pressure, serum PAPP-A, PIGF, BMI, nulliparity and a previous history of PE in previous pregnancy; however, PE developed in 32 patients. While 7321 patients were expected not to develop PE, two patients had a diagnosis of PE. As a result, the sensitivity and specificity of this model were calculated as 94.1% and 94.3%, respectively (28). In our study, when we classified the patients as group 1 (control group, n=168), group 2 (patients with mild PE and GHT; n=20) and group 3 (patients with severe PE and HELLP; n=5), median sEng value was 14.97 ng/mL in group 2 and 19.15 ng/mL in group 3, and a statistically significant difference was detected between the groups (p=0.001). sEng level in group 1 was higher than in group 2. PIGF level was relatively decreased and was 76.05 pg/mL in group 2 and 66.10 pg/mL in group 3, however, there was no statistically significant difference. Similar to the literature, sEng was statistically higher and PIGF was lower between group 2 and 3. Unlike the literature, low PIGF and high sEng levels were detected in the control group. The disproportionate distribution of cases between groups (168/5, 168/20) and fewer preeclamptic patients may be the reason of this situation. While PIGF and PAPP-A levels decrease in PE, sEng level increases. In our study, no statistically significant difference was found between the preeclamptic group and control group in terms of these markers. We consider that this result is due to the fact that the distribution of cases was disproportionate and the number of preeclamptic cases was less than the control group. However, in subgroup analysis, it was found that PIGF level in the group 3 was significantly decreased and sEng levels were increased compared to group 2. UtA PI value was higher in preeclamptic pregnant women compared to the control group. Similar results were obtained in our study. PI value in preeclamptic group was significantly higher compared to control group (p=0.023). When PI cut-off value was taken as >2.23 in PE prediction, the sensitivity and specificity were 42.31% and 82.10%, respectively. UtA Doppler examination is an effective diagnostic tool in PE prediction.

CONCLUSION

Since UtA Doppler screening is simple and noninvasive and brings very little extra time to the duration of screening, it may be included in the current sonographic examination. The sensitivity of UtA Doppler examination may be increased by adding one or more serum markers. Combinations provide an increase in the ability of prediction and determination compared to the tests used alone.

Ethics

Ethics Committee Approval: The study was approved by the KAEK (project no: 2013/100, date: 26.03.2013).

Informed Consent: Informed consent of all patients were taken.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.Y.K., Concept: Ş.Y.K., G.Y., Design: Y.Ç., M.B.Ç., G.Y., Data Collection or Processing: Ş.Y.K., Y.C., Analysis or Interpretation: Y.Ç., Ş.Y.K., Literature Search: Ş.Y.K., Y.C., G.Y., Writing: Ş.Y.K., G.Y.

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REFERENCES

1. ACOG Committee on Obstetric Practice. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 2002;77:67-75.
2. Caniggia I, Winter J, Lye SJ, Post M. Oxygen and placental development during the first trimester: implications for the pathophysiology of pre-eclampsia. Placenta 2000;21 Suppl A:25-30.
3. Gómez O, Figueras F, Martínez JM, del Río M, Palacio M, Eixarch E, et al. Sequential changes in uterine artery blood flow pattern between the first and second trimesters of gestation in relation to pregnancy outcome. Ultrasound Obstet Gynecol 2006;28:802-8.
4. Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. Prenat Diagn 2011;31:66-74.
5. Baumann MU, Bersinger NA, Surbek DV. Serum markers for predicting pre-eclampsia. Mol Aspects Med 2007;28:227-44.
6. Chaiworapongsa T, Romero R, Tarca AL, Kusanovic JP, Gotsch F, Mittal P, et al. A decrease in maternal plasma concentrations of sVEGFR-2 precedes the clinical diagnosis of preeclampsia. Am J Obstet Gynecol 2010;202:550.e1-10.
7. Luft FC. Soluble endoglin (sEng) joins the soluble fms-like tyrosine kinase (sFlt) receptor as a preeclampsia molecule. Nephrol Dial Transplant 2006;21:3052-4.
8. Al-Jameil N, Aziz Khan F, Fareed Khan M, Tabassum H. A Brief Overview of Preeclampsia. J Clin Med Res 2014;6:1-7.
9. Krantz D, Goetzl L, Simpson JL, Thom E, Zachary J, Hallahan TW, et al. Association of extreme first trimester free human chorionic gonadotropin-beta, pregnancy associated plasma protein A, and nuchal translucency with intrauterine growth restriction and other adverse pregnancy outcomes. Am J Obstet Gynecol 2004;191:1452-8.
10. Goetzinger KR, Singla A, Gerkowicz S, Dicke JM, Gray DL, Odibo AO. Predicting the risk of pre-eclampsia between 11 and 13 weeks' gestation by combining maternal characteristics and serum analytes, PAPP-A and free β-hCG. Prenat Diagn 2010;30:1138-42.
11. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122-31.
12. Sibai BM, Ramadan MK, Chari RS, Friedman SA. Pregnancies complicated by HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): subsequent pregnancy outcome and long-term prognosis. Am J Obstet Gynecol 1995;172:125-9.
13. Harrington K, Carpenter RG, Goldfrad C, Campbell S. Transvaginal Doppler ultrasound of the uteroplacental circulation in the early prediction of pre-eclampsia and intrauterine growth retardation. Br J Obstet Gynaecol 1997;104:674-81.
14. Melchiorre K, Wormald B, Leslie K, Bhide A, Thilaganathan B. First-trimester uterine artery Doppler indices in term and preterm pre-eclampsia. Ultrasound Obstet Gynecol 2008;32:133-7.
15. Napolitano R, Melchiorre K, Arcangeli T, Dias T, Bhide A, Thilaganathan B. Screening for preeclampsia by using changes in uterine artery Doppler indices with advancing gestation. Prenat Diagn 2012;32:180-4.
16. Nicolaides KH, Bindra R, Turan OM, Chefetz I, Sammar M, Meiri H, et al. A novel approach to first-trimester screening for early pre-eclampsia combining serum PP-13 and Doppler ultrasound. Ultrasound Obstet Gynecol 2006;27:13-7.
17. Poon LC, Maiz N, Valencia C, Plasencia W, Nicolaides KH. First-trimester maternal serum pregnancy-associated plasma protein-A and pre-eclampsia. Ultrasound Obstet Gynecol 2009;33:23-33.
18. Spencer K, Cowans NJ, Chefetz I, Tal J, Meiri H. First-trimester maternal serum PP-13, PAPP-A and second-trimester uterine artery Doppler pulsatility index as markers of pre-eclampsia. Ultrasound Obstet Gynecol 2007;29:128-34.
19. Di Lorenzo G, Ceccarello M, Cecotti V, Ronfani L, Monasta L, Vecchi Brumatti L, et al. First trimester maternal serum PIGF, free β-hCG, PAPP-A, PP-13, uterine artery Doppler and maternal history for the prediction of preeclampsia. Placenta 2012;33:495-501.
20. Spencer K, Yu CK, Cowans NJ, Otigbah C, Nicolaides KH. Prediction of pregnancy complications by first-trimester maternal serum PAPP-A and free beta-hCG and with second-trimester uterine artery Doppler. Prenat Diagn 2005;25:949-53.
21. Lai J, Syngelaki A, Poon LC, Nucci M, Nicolaides KH. Maternal serum soluble endoglin at 30-33 weeks in the prediction of preeclampsia. Fetal Diagn Ther 2013;33:149-55.
22. Kusanovic JP, Romero R, Chaiworapongsa T, Erez O, Mittal P, Vaisbuch E, et al. A prospective cohort study of the value of maternal plasma concentrations of angiogenic and anti-angiogenic factors in early pregnancy and midtrimester in the identification of patients destined to develop preeclampsia. J Matern Fetal Neonatal Med 2009;22:1021-38.
23. Levine RJ, Thadhani R, Qian C, Lam C, Lim KH, Yu KF, et al. Urinary placental growth factor and risk of preeclampsia. JAMA 2005;293:77-85.
24. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. Fetal Diagn Ther 2013;33:8-15.
25. Diguisto C, Piver E, Gouge AL, Eboue F, Vaillant CL, Maréchaud M, et al. First trimester uterine artery Doppler, sFlt-1 and PlGF to predict preeclampsia in a high-risk population. J Matern Fetal Neonatal Med 2017;30:1514-9.
26. Li L, Zheng Y, Zhu Y, Li J. Serum biomarkers combined with uterine artery Doppler in prediction of preeclampsia. Exp Ther Med 2016;12:2515-20.
27. O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, Wright A, et al. Accuracy of competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2017;49:751-755.
28. Poon LC, Kametas NA, Maiz N, Akolekar R, Nicolaides KH. First-trimester prediction of hypertensive disorders in pregnancy. Hypertension 2009;53:812-8.

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Evaluation of Complete Blood Count Parameters Before and After Appendectomy

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Abstract

Objective: Acute appendicitis (AA) is the most common cause of intra-abdominal surgery worldwide and its diagnosis continues to be problematic despite advanced technology and diagnostic methods. Easily accessible, economical and non-invasive tests are still under investigation for the diagnosis and after surgery. The purpose of this study was to review postoperative changes in patients' complete blood count (CBC) parameters.

Methods: The research was performed as a single-center, retrospective, cross-sectional study. After obtaining the approval of the ethics committee, the data obtained from patients aged over 18, who underwent appendectomy between January 1, 2015 and November 30, 2017, and who were diagnosed with histopathologically confirmed AA, were retrospectively examined. Wilcoxon test was used in statistical analysis to compare pre- and post-operative changes in CBC parameters. A p value of less than 0.05 was considered statistically significant.

Results: Men constituted 50% (n=726) of the 1452 enrolled patients. The mean age of the patients was 32.3±16.1 years. Statistically significant differences were determined between pre-operative and post-operative leukocyte white blood cell, lymphocyte, hemoglobin, hematocrit, plateletcrit and mean platelet volume values. Mean neutrophil and platelet count values decreased in the post-operative period, although these decreases were not statistically significant. No statistically significant difference was determined between pre-operative and post-operative neutrophil/lymphocyte ratio (NLR) values.

Conclusion: Dilutional changes in CBC parameters may occur following fluid therapy in the post-operative period. We also conclude that NLR is not affected by fluid treatment and may be a valuable parameter in monitoring post-appendectomy infection.

Keywords: Acute appendicitis, blood count, neutrophil/leukocyte ratio, mean platelet volume, platelet count

INTRODUCTION

Acute appendicitis (AA) ranks first among intra-abdominal pathologies requiring surgery (1). Mortality and morbidity are low if surgery is performed early (2). Typical AA findings include right lower quadrant tenderness, anorexia, nausea, pain migration and rebound positivity on physical examination (3). The presence of atypical findings depending on the location of the appendix may cause AA to be missed and complications may develop. Some patients diagnosed with AA may present to emergency departments with non-specific symptoms or additional symptoms of other diseases. AA cases presenting with right upper quadrant pain or anuria alone have also been reported. AA has also been reported in patients presenting with findings such as psoas abscess in the gluteal region or cellulitis (4-6). Therefore, post-operative parameters are needed for use in the clinical follow-up of AA patients. Blood tests such as leukocyte count white blood cell (WBC), neutrophil/lymphocyte ratio (NLR) and C-reactive protein (CRP) are used in addition to abdominal ultrasonography in the diagnosis of AA, but these may not always be sufficient for a definitive diagnosis. In this case, intravenous contrast-enhanced abdominal computed tomography is recommended (3,7,8). Recent studies have shown that platelet markers such as mean platelet volume (MPV), platelet distribution width (PDW) and platelet count are useful in the diagnosis of AA. Platelet activation markers such as plateletcrit (PCT), MPV and PDW are associated with platelet morphology and proliferation kinetics. These markers permit low-cost focusing on diagnostic and prognostic values and broad clinical investigation (9,10). The aim of this study was to

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assess whether the regression of preexisting infection before appendectomy could be determined by evaluating complete blood count (CBC) parameters after appendectomy.

METHODS

This research was performed as a single-center, retrospective, cross sectional study. After receiving the approval of the local ethics committee of Ankara Training and Research Hospital (approval no: 13122017/0028.311), the data obtained from patients aged over 18, who underwent appendectomy between January 1, 2015 and November 30, 2017, and who were diagnosed with histopathologically confirmed AA, were retrospectively examined hospital records. Pregnant subjects and patients with liver or kidney failure, malignancy or known hematological disease, patients under 18 of age and patients with missing data were excluded from the study.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) 15.0 for Windows was used for statistical analysis. Visual (histogram, probability, and plot) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests) were used to assess whether the variables were normally distributed. Descriptive analyses were expressed using median and 25-75 percentiles. Since blood count parameters were not normally distributed, non-parametric tests were used to compare them, similar to gradient variables. Wilcoxon test was used to compare changes in pre-operative and post-operative blood count parameters. A p value less than 0.05 was considered statistically significant.

RESULTS

We identified 1837 patients who underwent appendectomy between January 1, 2015 and November 30, 2017 with histopathologically confirmed AA. Patient data was examined using the automation information processing data. One hundred and eighty-five patients were excluded due to missing data in 77 patients, malignancy or hematological diseases in 44 patients, being under 18 years in 38 patients, liver or kidney failure in 19 patients, and pregnancy in seven patients. Therefore, 1452 patients were eventually enrolled. Seven hundred and twenty-six (50%) patients were female and 726 (50%) were male, with a mean age of 32.3±16.1 years (range, 18-43 years). There was no statistically significant between the genders in terms of age (p>0.05). The mean pre-operative CBC parameters were as follows: WBC count=10.200/mm^3 (range, 39.800-10.200/mm^3), lymphocyte count=2000/mm^3 (range, 1320-3570/mm^3), neutrophil count=5500/mm^3 (range, 1780-5380/mm^3), hemoglobin (Hb)=14.1 g/dL (range, 14.1-18.1 g/dL), hematocrit (Hct)=41.2% (range, 43.5-53.7%), NLR=2.24, PCT=0.23% (range, 0.15%-0.7%), PDW=12.00 fL (range, 9-19 fL), MPV=8.60 fL (range, 6.8-10.8 fL) and mean platelet count=248.000/mm^3 (range, 142.000-424.000/mm^3).

The mean post-operative CBC parameters were as follows: WBC count=7600/mm^3, lymphocyte count=1900/mm^3, neutrophil count=4900/mm^3, Hb=13.6 g/dL, Hct=41.4%, NLR=2.37, PCT=0.19%, PDW=11.70 fL, MPV=8.00 fL and platelet count =241.000/mm^3. The mean pre-operative WBC, lymphocyte, Hb, Hct, PCT and MPV values were significantly higher than post-operative values (p<0.001). A statistically insignificant decrease was observed in postoperative mean neutrophil, PDW and platelet count compared to pre-operative levels (p>0.05). There was no statistically significant difference between pre-operative and post-operative NLR values (p>0.05). Mean pre-operative and post-operative blood count parameters are shown in Table 1.

DISCUSSION

All platelet parameters such as PDW, MPV, PCT and platelet counts decreased between pre- and post-operative values. However, only the decreases in PCT and MPV values were statistically significant.

AA is the most common cause of intra-abdominal surgery. It is also one of the most common reasons for admissions to the emergency department, and the search for a rapid and easily performed test for the diagnosis of AA continues. Contemporary

Table 1. Mean complete blood count parameters in pre-operative and post-operative periods

	Pre-operative	Post-operative	p
White blood cell (/mm^3)	10.20	7.60	<0.001
Lymphocyte (/mm^3)	2.00	1.90	<0.001
Neutrophil (/mm^3)	5.50	4.90	0.035
Neutrophil/lymphocyte ratio	2.24	2.37	0.228
Hematocrit (%)	41.20	41.40	<0.001
Hemoglobin (g/dL)	14.10	13.60	<0.001
Platelet (/mm^3)	248.000	241.000	0.612
Plateletcrit (%)	0.23	0.19	<0.001
Platelet distribution width (fL)	12.00	11.70	0.200
Mean platelet volume (fL)	8.60	8.00	<0.001

studies have shown that platelet markers such as MPV, PDW and PCT can be used both in diagnosis and in predicting the prognosis of AA (11-13). However, the results of platelet markers in the diagnosis of AA are inconsistent. In a study of 503 subjects, Narci et al. (14) concluded that MPV values increased in AA patients. In contrast, in a study conducted in 2015, Kılıç et al. (15) reported a statistically significant decrease in MPV values in AA patients. There are other studies supporting this conclusion (11,16,17). In contrast to both studies, other studies with larger patient groups reported no changes in MPV values (13,18,19). In a study of 295 patients in 2015, Uyanik et al. (20) reported a statistically significant decrease in MPV values together with a decrease in PDW. In contrast, Fan et al. (17) reported a statistically significant increase in PDW values and a statistically significant increase in MPV values in AA patients. In contrast to several previous studies, our findings indicate that platelet markers such as PDW, PCT and MPV are not useful in the diagnosis of AA and in predicting its severity, since they exhibit a hemodilutional decrease related to hydration therapy. Since no information was available regarding whether our patients were complicated or uncomplicated in the pre-operative period, the antibiotic use status of the patients is unknown. Based on mean post-operative data, WBC, neutrophil and lymphocyte counts decreased. This can be attributed to hemodilution as well as AA being an infection that heals in the post-operative period. Therefore, it is not surprising that a decrease should be observed in leukocytes, which are one of the strongest markers of infection. Since a decrease was observed in all CBC parameters (including Hb, Hct, platelets and lymphocytes), we concluded that these values tended to decrease secondary to hemodilution. Normovolemic hemodilution with crystalloid or colloid solutions based on a calculation of blood loss during surgery is a method that has been applied for many years (21,22). A relative decrease in blood cell components due to a hemodilution-related increase in blood plasma volume is not surprising. Our study results seem to be compatible with hemodilution. Under these circumstances, it would not therefore be right to expect an increase in CBC parameters of WBC or neutrophil count alone. Since the patient's blood parameters decrease with hemodilution in the post-operative period, they will appear decreased or normal after the test, even if the WBC count increases in association with infection. A hemodilution-related decrease occurs in both neutrophil and lymphocyte counts. However, this decrease did not cause a statistically significant decrease in NLR. Therefore, we concluded that the NLR was not affected by hemodilution.

In recent years, NLR has been regarded as more effective than WBC or CRP alone in determining or following-up infection (7,23,24). Our results support the idea that NRL is more valuable than WBC or neutrophil counts in monitoring infections since it is not affected by hemodilution.

Study Limitations

Due to the retrospective nature of our study, our inability to access data for several patients resulted in a decrease in the number of patients. One of the main limitations of this study is that patients taken for appendectomy were not classified according to severity of the disease in the pre-operative period or according to the development of complications. Another limitation was that CRP values were not examined postoperatively while CBC values were investigated. Correlation analysis between changes in CRP values and blood count values may represent the subject of another study.

CONCLUSION

The blood parameters of the patients may be diluted due to the fluid therapy applied in the post-operative period. We also concluded that NLR was not affected by fluid therapy and might be a valuable parameter in monitoring infection after appendectomy. Moreover, platelet markers such as PDW, MPW and platelet count are not useful parameters in the diagnosis of AA. Further studies with larger patient groups are now needed to support our findings.

Ethics

Ethics Committee Approval: Approval of the local ethics committee of Ankara Training and Research Hopital (approval no: 13122017/0028.311).

Informed Consent: Informed consent form was obtained from all patients included in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.K., Concept: A.S.Y., Design: T.E., Data Collection or Processing: T.E., Analysis or Interpretation: B.K., Literature Search: A.S.Y., Writing: B.K.

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REFERENCES

1. Bachmann LM, Bischof DB, Bischofberger SA, Bonani MG, Osann FM, Steurer J. Systematic quantitative overviews of the literature to determine the value of diagnostic tests for predicting acute appendicitis: study protocol. BMC Surg 2002;2:2.

2. Omundsen M, Dennett E. Delay to appendicectomy and associated morbidity: a retrospective review. ANZ J Surg 2006;76:153-5.

3. Lee SL, Ho HS. Acute appendicitis: is there a difference between children and adults? Am Surg 2006;72:409-13.

4. Kaykısız EK. (19-22 Nisan 2018). Bilinen Bir Tanının Az Bilinen Prezentasyonu: Akut Kolesistiti Taklit Eden Bir Akut Apandisit Vakası. B. Cander Editörler, 14. Ulusal Acil Tıp Kongresi (94), Antalya, Acil Tıp Uzmanları Derneği.

5. Choi SB, Han HJ, Kim WB, Song TJ, Choi SY. A case of a recurrent iliopsoas abscess masking a complicated appendicitis successfully treated by a laparoscopic approach. Surg Laparosc Endosc Percutan Tech 2010;20:e69-72.

6. Kuday Kaykisiz E, Yildirim MB, Dadali E, Kaykisiz H, Ünlüer EE. Different manifestation of a familiar diagnosis: From anuria to acute appendicitis. Am J Emerg Med 2018;36:910.e5-910.e7.

7. Kaykısız EK, Akyol PY, Karakaya Z, Payza U, Topal FE. Neutrophil/lymphocyte ratio is a valuable data to reduce negative laparotomy rates in emergency department. Bio Med Res 2017;28:8438-42.

8. Börekçi H, Karacabey S, Sipahi M, Özdemir ZT, Erkoç MF. A rare case: Retrocecal appendicitis adherent to the liver capsule. Turk J Surg 2015;33:227-9.

9. Yardımcı S, Uğurlu MÜ, Coşkun M, Attaallah W, Yeğen ŞC. Neutrophil-lymphocyte ratio and mean platelet volume can be a predictor for severity of acute appendicitis. Ulus Travma Acil Cerrahi Derg 2016;22:163-8.

10. Bozkurt S, Köse A, Erdogan S, Bozali GI, Ayrik C, Arpaci RB, et al. MPV and other inflammatory markers in diagnosing acute appendicitis. J Pak Med Assoc 2015;65:637-41.

11. Yiğitler C, Uyar C, Baylan O, Ongörü O, Güleç B, Akut apandisit ön tanısıyla ameliyat edilen hastalarda C-reaktif proteinin tanısal değeri ve postoperatif doğal seyri. Turk j surg 2002;8: 224-33.

12. Daskalakis K, Juhlin C, Påhlman L. The use of pre- or postoperative antibiotics in surgery for appendicitis: a systematic review. Scand J Surg 2014;103:14-20.

13. Albayrak Y, Albayrak A, Albayrak F, Yildirim R, Aylu B, Uyanik A, et al. Mean platelet volume: a new predictor in confirming acute appendicitis diagnosis. Clin Appl Thromb Hemost 2011;17:362-6.

14. Narci H, Turk E, Karagulle E, Togan T, Karabulut K. The role of mean platelet volume in the diagnosis of acute appendicitis: a retrospective case-controlled study. Iran Red Crescent Med J 2013 ;15:e11934.

15. Kılıç TY, Yesilaras M, Karaali C, Atilla OD, Sezik S. Diagnostic value of mean platelet volume in acute appendicitis. J Clin Anal Med 2015;1-3.

16. Aktimur R, Cetinkunar S, Yildirim K, Özdas S, Aktimur SD, Mean platelet volume is a significant biomarker in the differential diagnosis of acute appendicitis. Inf Cell Sig 2015;2:e930.

17. Fan Z, Pan J, Zhang Y, Wang Z, Zhu M, Yang B, et al. Mean platelet volume and platelet distribution width as markers in the diagnosis of acute gangrenous appendicitis. Dis Markers 2015;2015:542013.

18. Tanrikulu CS, Tanrikulu Y, Sabuncuoglu MZ, Karamercan MA, Akkapulu N, Coskun F. Mean platelet volume and red cell distribution width as a diagnostic marker in acute appendicitis. Iran Red Crescent Med J 2014;16:e10211.

19. Bilici S, Sekmenli T, Göksu M, Melek M, Avci V. Mean platelet volume in diagnosis of acute appendicitis in children. Afr Health Sci 2011;11:427-32.

20. Uyanik B, Kavalci C, Arslan ED, Yilmaz F, Aslan O, Dede S, et al. Role of mean platelet volume in diagnosis of childhood acute appendicitis. Emerg Med Int 2012;2012:823095.

21. Dinc B, Oskay A, Dinc SE, Bas B, Tekin S. New parameter in diagnosis of acute appendicitis: platelet distribution width. World J Gastroenterol 2015;21:1821-6.

22. Yılmaz Y, Kara F, Gümüşdere M, Arslan H, Üstebay S. The platelet indices in pediatric patients with acute appendicitis. Int J Res Med Sci 2015;3:1388-91.

23. Wullstein C, Barkhausen S, Gross E. Results of laparoscopic versus conventional appendectomy in complicated appendicitis. Dis Colon Rectum 2001;44:1700-5.

24. Lin HF, Wu JM, Tseng LM, Chen KH, Huang SH, Lai IR. Laparoscopic versus open appendectomy for perforated appendicitis. J Gastrointest Surg 2006;10:906-10.

ORIGINAL ARTICLE

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Evaluation of Dynamic Hyperinflation with Negative Expiratory Pressure Method in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Objective: Chronic Obstructive Pulmonary disease (COPD) is a disease characterized by progressive airflow limitation, which is not fully reversible. Expiratory flow limitation (EFL) is the most common cause of dynamic hyperinflation (DH) and increased respiratory workload in COPD. In our study, the relationship between negative expiratory pressure (NEP) and all pulmonary function tests, especially inspiratory capacity (IC), was investigated in the examination of DH in COPD patients.

Methods: Thirty four COPD patients with a mean forced expiratory volume in one second (FEV1) of 38.9±12.7% and 15 healthy subjects were included in the study. Pulmonary function tests and NEP were performed in all COPD patients.

Results: In 16 COPD patients (47.1%), EFL was positive with NEP. When pulmonary function tests of EFL positive and EFL negative patients were compared, significant differences were found only in obstruction parameters such as FEV1 and forced expiratory flow 25-75, but no difference was found with lung volumes and diffusion test. However, there was a statistically significant correlation between IC and FVC (mL and % predicted), FEV1 (% predicted) and lung volumes (mL and % predicted) and FRC (mL) ($p<0.05$). There was a negative but statistically insignificant correlation between IC and presence of flow limitation ($p>0.05$).

Conclusion: We think that NEP application in COPD patients does not provide additional information about DH and that IC is the best predictor of DH.

Keywords: Chronic Obstructive Pulmonary disease, inspiratory capacity, negative expiratory pressure

INTRODUCTION

Chronic Obstructive Pulmonary disease (COPD) is an inflammatory disease caused by various harmful particles and gases, and is characterized by progressive airflow limitation that is not fully reversible. Airflow limitation in COPD develops as a result of small airway disease and parenchymal destruction. While chronic inflammation leads to remodeling and narrowing of the small airways, the decrease in elastic recoil as a result of parenchymal damage makes it difficult to maintain the patency of the airways during expiration (1). In patients with COPD, the delay in lung emptying due to decreased expiratory flow during spontaneous breathing prevents the lungs from passively reaching the functional residual capacity (FRC) level before the next inspiration. As a result, the end-expiratory lung volume exceeds the FRC level. Pulmonary volume increases in COPD due to reduced elastic recoil and airway resistance. This leads to a new equilibrium at a higher level than FRC at the end of the expiration. This phenomenon is called dynamic hyperinflation (DH) (2). In COPD, pulmonary function tests (PFT) are the most commonly used laboratory methods in the diagnosis, evaluation of disease progression and prognosis and severity of the disease, and monitoring the treatment response (3). Spirometric examination is mandatory to confirm the diagnosis of COPD. It has been reported that inspiratory capacity (IC) is guiding for demonstrating the presence of dynamic collapse in the respiratory tract in COPD (3). IC is the volume of gas that can be inspired following a normal, quiet expiration. It includes tidal volume (TV) and inspiratory reserve volume. It constitutes approximately 75% of vital capacity. In recent studies, it has been

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shown that IC is an important parameter in demonstrating the presence of DH in the respiratory tract in COPD (4,5). The most important change that can be detected in spirometry in COPD is expiratory flow limitation (EFL). Negative expiratory pressure (NEP) technique is one of the simplest ways to demonstrate EFL, which is the most important cause of DH. The NEP technique usually involves applying a negative pressure around -5 cm H_2O into the mouth during tidal expiration and comparing the resulting flow-volume (F-V) loop with the previously made control expiratory F-V loop. In COPD patients, NEP technique can be applied during mechanical ventilation, exercise, dyspneic and orthopneic state, before and after bronchodilatation, and in different positions. Maximal expiratory flow can be achieved even at rest in conditions with airflow limitations, such as COPD. In patients with COPD, it is seen that the volume of gas remaining in the lungs increases at the end of expiration, especially during exercise. As a result, the expiratory reserve volume increases, the inspiratory reserve volume decreases, and the IC decreases. This is due to the collapse of the peripheral airways and increased expiratory reserve volume due to increased dynamic collapse during exercise. Increase in TV during exercise can reach up to IC value in COPD patients. In addition, flow velocities during TV can reach the flow velocities at maximal expiration loop. The reflection of this in the F-V loop is that the TV curve plotted during the exercise coincides with the maximal expiration curve, thus EFL being positive. Presence of EFL in COPD patients leads to DH, increased respiratory work, impaired inspiratory muscle function and progressive dyspnea (4-7). In this study, we aimed to investigate the relationship between NEP and PFT and lung volumes in the examination of DH in patients with COPD.

METHODS

Thirty four stable patients with COPD at stage 2 and 3 (1) and 15 healthy subjects without smoking history and respiratory disease were included in the study. Patients with COPD were on inhaled long-acting beta-agonists, anticholinergic, inhaler steroid and oral theophylline with inhaled short-acting beta-agonists. Stable period was defined as not having an acute exacerbation of COPD until four weeks prior to enrollment. According to this definition, the presence of two of the three criteria, including worsening in dyspnea, increase in purulence or amount of sputum, makes the diagnosis of COPD exacerbation clinically. Patients with known pulmonary disease other than COPD and who had received oral corticosteroid treatment in the last two months were excluded from the study. The control group was selected from the patients who applied to the chest diseases outpatient clinic and did not have any pathology in their examinations. Informed consent form was obtained from all subjects at the beginning of the study. All patients in the COPD and control groups were evaluated by PFT (spirometer, lung volumes) in sitting position and EFL examination by NEP in the respiratory laboratory. The study was approved by Ethics Board of Department of Chest Disesase (1724-2004).

Pulmonary Function Tests

Spirometric examinations were performed in the respiratory laboratory using Sensor Medics Vmax Series 22. Forced spirometric tracing was obtained by prompting the patient to inspire to the level of total lung capacity, followed by rapid and forced ventilation. The curve was plotted at least three times while the nose was closed and the maximum FVC and forced expiratory volume in one second (FEV1) values of the three curves were used in our study. Total lung volume and residual volume measurements were made using Nitrogen Washout method (8).

Negative Expiratory Pressure

In our study, NEP method was used to detect EFL. The tools required for the application of this method are as follows:

- Pneumatograph

- Differential pressure transducer

- Negative pressure generating device

- Data collection system

A plastic mouthpiece is connected to the T tube and pneumotograph. One end of the T tube is open to the atmosphere. The other end is exposed to the negative pressure created by the venturi apparatus or vacuum generator by means of a valve (solenoid valve, Hans Rudolph valve). When the valve is opened, NEP is applied to the airway. Airway flow (V°) is measured by pneumotograph, while airway opening pressure is simultaneously measured by the side port of the mouthpiece. Volume (V) is obtained from numerical integration of flow signals in data acquisition systems. The F-V loop obtained by NEP is overlaid with the F-V loop obtained by the previous normal respiration. Data analysis is performed by visual evaluation of two F-V loops (9). In our study, a Micro NEP brand NEP device was used (Micro Medical Ltd. Kent, UK).

The results obtained from the NEP technique are interpreted in three ways:

- No flow limitation

- Flow limitation during one part of expiration

- Limited flow throughout expiration. Flow limitation of expiration is given as a percentage of control TV % (9).

As shown in Figure 1, if NEP application leads to increased flow through the entire control VT, flow is not limited (NEP example, left panel). On the contrary, if the F-V loop formed during expiration with NEP intersects with some or all of the control F-V loop, the patient has EFL (NEP example, middle and right panel) (Figure 1).

Statistical Analysis

SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, Illinois, USA) for Windows 10.0 was used for data analysis. The determination of the number of samples in our study was based on the studies in the literature in which the NEP method was examined in COPD cases. The post hoc power analysis at the end of the study revealed a 100% power for FVC with 95% confidence interval. Normality of the data was evaluated by Kolmogorov-Smirnov test. Mann-Whitney U test was used to compare the parameters. Pearson method was used for correlation analysis. The values were expressed as mean ± standard deviation, and non-normally distributed data were expressed as median and interquartile range 25-75. P<0.05 was considered statistically significant.

RESULTS

Demographic characteristics of the patients are shown in Table 1. Regarding mean ages of the groups, no statistically significant difference was found between patient and control groups (p>0.05).

Spirometric values of patient and control groups are presented in Table 2 and lung volumes are presented comparatively in Table 3. NEP technique was applied to all participants. EFL was not detected in any of the subjects in the control group. EFL was positive in 16 COPD patients (47.1%). When the EFL was expressed as a percentage of TV, the mean EFL value was 31.44±38%. The study group was divided into two groups as EFL positive and negative, and the variables between the two groups were examined. There was no statistically significant difference between the two groups in terms of age, amount of smoking and disease duration (p>0.05). Spirometry values of the group with positive and negative EFL are presented in Table 4, and a statistically significant difference was found between FEV1 (%) and forced expiratory flow (FEF) 25-75% (%) values. The comparison of lung volumes of the group with and without EFL is shown in Table 5 and no statistically significant difference was found between the two groups. Table 6 shows the correlation coefficients of IC values measured in the COPD group with age, disease duration, presence of EFL, PFT and lung volumes. As shown in the Table 6, significant correlations were found

Table 1. Demographic characteristics of patient and control groups

	COPD group	Control group
Number of cases (F, M)	34 (2F, 32M)	15 (2F, 13M)*
Age (years)	66.3±7.9	66.7±7.7**
Disease duration (years)	7.97±5	-
Smoking (pack/year)	57.6±29.7	-
Number of patients who stopped smoking	31	-
Smoking cessation period (years)	4.1±4.7	-

COPD: Chronic Obstructive Pulmonary disease, F: Female, M: Male
*p>0.05, **p>0.05

Table 2. Pulmonary function test results in patient and control groups

Pulmonary function tests	Patient group	Control group
FVC (mL)	2365±643	3975±629*
FVC (%)	72.1 (61.1-81.2)	102.3 (94.6-110.2)*Ŧ
FEV1 (mL)	1001±300	3258±551*
FEV1 (%)	38.9±12.7	104.3±13.3*
FEV1/FVC (%)	42.8±7.6	79.7±5.2*
FEF %25-75 (L/sn)	0.25 (0.11-0.47)	3.4 (2.46-4.8)*Ŧ
FIV1 (mL)	1800 (1212-2500)	3480 (2600-4300)*Ŧ

FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, FEF: Forced expiratory flow, FIV1: Forced inspiratory volume in one
*p<0.000, Ŧ: Mann-Whitney U test used
The data in parentheses are median and interquartile range 25-75

Table 3. Lung volumes of patient and control groups

Lung volumes	Patient group	Control group
TLC (mL)	6610±1896	6157±776
TLC (%)	109.5±26.3	97.5±10*
RV (mL)	3980 (2504-4904)	2261 (1724-2803)**Ŧ
RV (%)	169.1±50.9	102.3±13.6**
RV/TLC (%)	59.6±8.9	35.2±3.3**
VC (mL)	2604±747	3919±554**
VC (%)	74.4±21.9	96.8±10.7**
IC (mL)	1885±499	3023±723**
FRC (mL)	4699±1643	2951±539**
FRC (%)	140.5±42.6	94.6±14.8**
ERV (mL)	705 (312-1115)	702 (524-1064)Ŧ

TLC: Total lung capacity, RV: Residual volume, VC: Vital capacity, IC: Inspiratory capacity, FRC: Functional residual capacity, ERV: Expiratory reserve volume
The data in parentheses are median and interquartile range 25-75
*p<0.05, **p<0.000, Ŧ: Mann-Whitney U test used

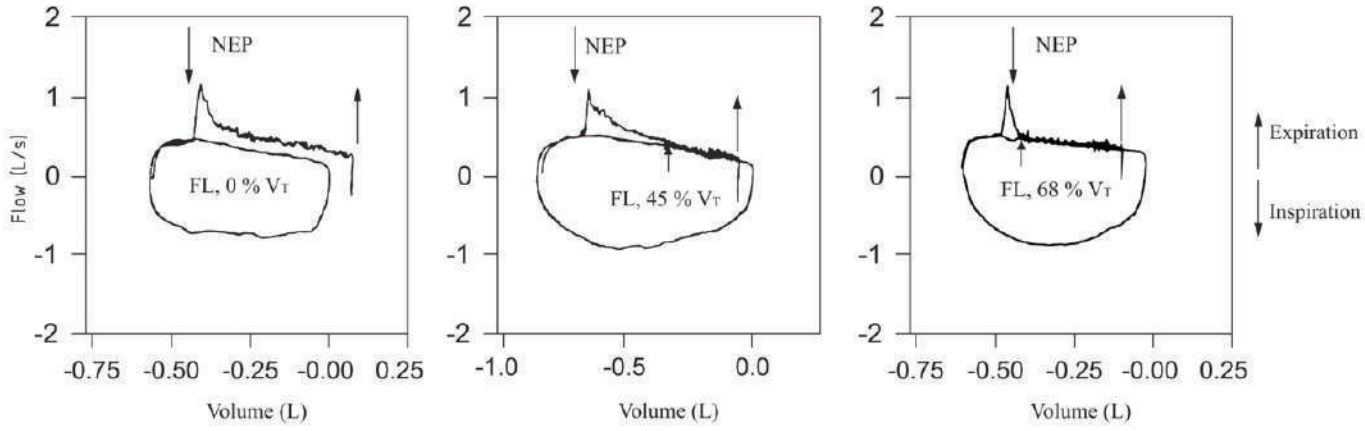

Figure 1. Negative expiratory pressure examples of cases with and without flow limitation (5)
NEP: Negative expiratory pressure

Table 4. Pulmonary function test values of the group with negative and positive expiratory flow limitation

Pulmonary function tests	EFL negative	EFL positive
FVC (mL)	2459.4±623.6	2260.6±6669.6
FVC (%)	76.7 (51.2-98.3)	68.2 (49.2-87.3)Ŧ
FEV1 (mL)	1080±326.5	913.7±248.3
FEV1 (%)	43.5±14.5	33.8±8*
FEV1/FVC (%)	44.6±8.8	40.9±5.5
FEF 25-75% (L/s)	0.37 (0.22-0.53)	0.29 (0.21-0.49)Ŧ
FEF 25-75% (%)	12.8 (7.3-16.4)	9.4 (6.4-13.4)*Ŧ

FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, FEF: Forced expiratory flow
The data in parentheses are median and interquartile range 25-75
*p<0.05, Ŧ: Mann-Whitney U test used

Table 5. Pulmonary function test values of the group with negative and positive expiratory flow limitation and positive group

Pulmonary volumes	EFL negative	EFL positive
TLC (mL)	6920±1605	6223±2219*
TLC (%)	116.3±20.4	101±31.1*
RV (mL)	4276 (3325-5135)	3620 (2704-4226)*Ŧ
RV (%)	180.3±39.6	155.1±61.2*
RV/TLC (%)	62±6.6	56.5±10.6*
FRC (mL)	4954±1385	4382±1935*
FRC (%)	148.4±33.4	130.6±51.7*
IC (mL)	1921±475	1843±543*

TLC: Total lung capacity, RV: Residual volume, IC: Inspiratory capacity, FRC: Functional residual capacity, EFL: Expiratory flow limitation
*p>0.05, Ŧ: Mann-Whitney U test used
The data in parentheses are median and interquartile range 25-75

between IC and PFT and lung volumes. However, a negative but not statistically significant correlation was found between IC and EFL.

Table 6. Parameters correlating with inspiratory capacity in Chronic Obstructive Pulmonary disease group

Parameters	Correlation coefficients (r)
Age (years)	0.242
Disease duration (years)	-0.373
Presence of expiratory flow limitation	-0.202
FVC (%)	0.592***
FEV1 (%)	0.519**
FEV1 /FVC (%)	0.047
PEF (%)	0.666***
TLC (%)	0.573**
VC (mL)	0.797***
VC (%)	0.599***
FRC (mL)	0.438*
RV (mL)	0.484*
RV (%)	0.429*

FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, PEF: Peak expiratory flow, VC: Vital capacity, TLC: Total lung capacity, RV: Residual volume
Pearson correlation analysis was used
*p<0.05, **p<0.01, ***p<0.001

DISCUSSION

The main pathophysiological point of COPD is the presence of EFL. The most important cause of EFL is DH and increased respiratory workload. It has been shown that IC is the best predictor for reflecting the presence of DH in the respiratory tract, especially in studies evaluating exercise intolerance. In recent years, the use of IC in place of FEV1 has also been recommended to evaluate the efficacy of bronchodilator therapy (10,11). One of the simplest ways to show EFL, which is the most important cause of DH, is the implementation of NEP. In our study, 16 (47.1%) of 34 patients with moderate and severe COPD had positive EFL in sitting position and 18 (52.9%) were EFL negative.

NEP application of two COPD cases with and without EFL is shown in Figure 2 and Figure 3. Koulouris et al. (12) applied NEP in 26 ambulatory COPD patients with a mean FEV1 of 60±22% and found EFL negative in seven patients (26.9%). Eltayara et al. (13) found that EFL was negative in 26 cases (22.2%) after the application of NEP in 117 patients with stable COPD, including 75 male and 42 female patients. In both studies, NEP was performed in the same patient in both sitting and supine positions. In both studies, no flow limitation was detected in both sitting and supine positions of the cases with negative EFL. In our study, since the application of NEP was performed only in the sitting position, the rate of negative EFL was found to be higher when compared with the literature. In two studies that examined the EFL by NEP only in the sitting position in the literature, the rates of positive EFL were found to be high as in our study. Positive EFL rate was 55.7% in the study conducted by Diaz et al. (14) and 61.1% in the study conducted by Tantucci et al. (15). In our study, when all PFT of the patients with positive and negative EFL were compared, only FEV1% predicted and FEF 25-75% predicted were found to be statistically significantly different ($p<0.05$). Studies in the literature have shown that FEV1% predicted is significantly lower in COPD patients with positive EFL (13,16).

By examining the presence of EFL by using NEP method, information about DH can be obtained. In most of the studies on this subject, the presence of EFL in COPD patients was found to be significantly correlated with increased lung volumes. Koulouris et al. (16) found statistically significant difference in total lung capacity (TLC) %, RV%, RV/TLC, FRC% values, while Diaz et al. (17) found statistically significant difference in other parameters except TLC%. Boni et al. (18) found no significant difference in lung volumes between the groups with and without EFL, as in our study (14).

In recent studies, the importance of IC, which is a new parameter that correlates with dyspnea, has been emphasized in assessing the efficacy of pharmacological and surgical treatment in patients with COPD, identifying physiological changes during exercise (3). In our study, the relationship of IC with other lung volumes and NEP was evaluated in the evaluation of DH. There was a statistically significant correlation between IC and airway obstruction parameters such as FVC% predicted, FEV1% predicted and peak expiratory flow % predicted ($p>0.05$). Diaz et al. (17) Tantucci et al. (14) and Koulouris et al. (16) found a statistically significant negative correlation between IC and the presence

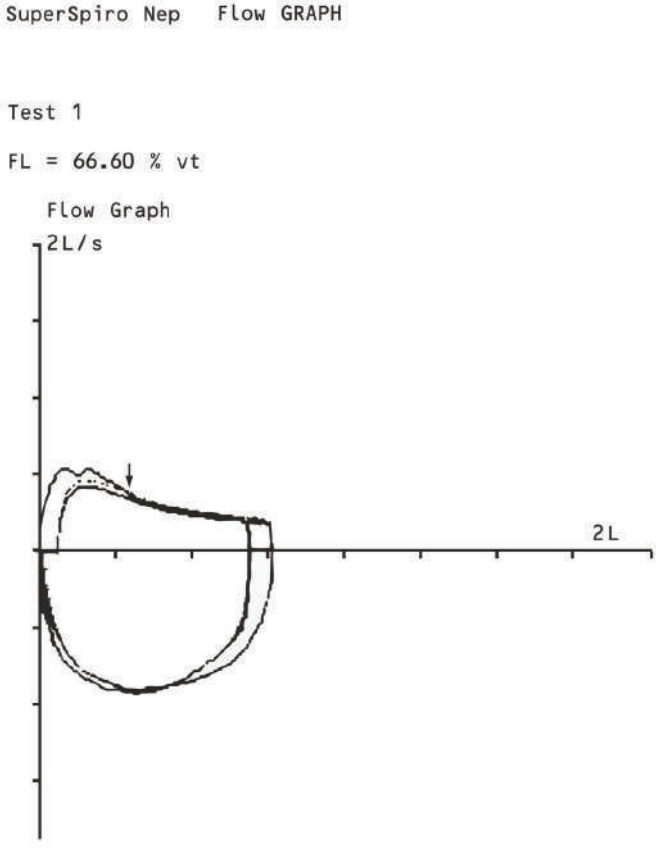

Figure 2. Negative expiratory pressure application of Chronic Obstructive Pulmonary disease patient with expiratory flow limitation

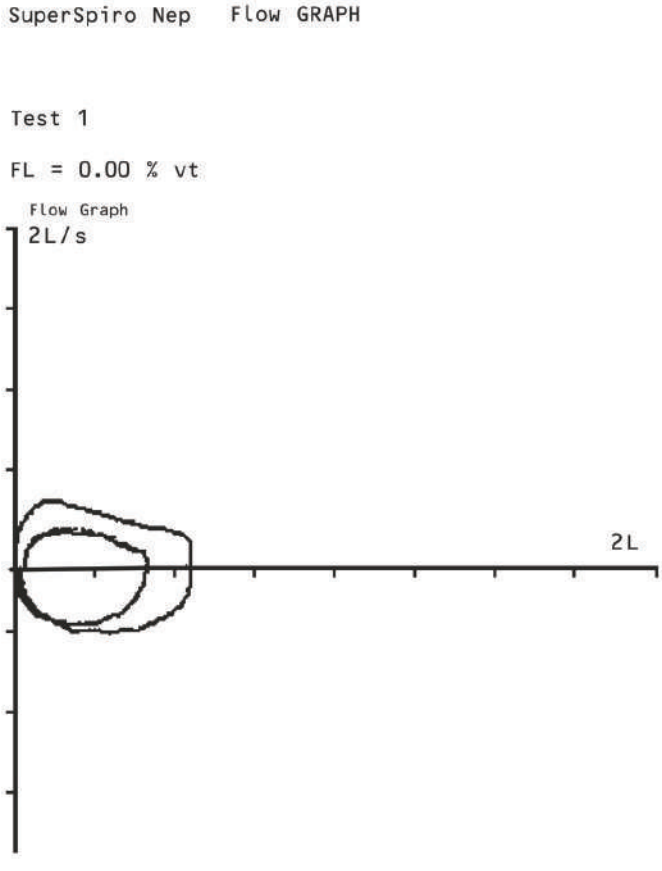

Figure 3. Negative expiratory pressure application of Chronic Obstructive Pulmonary disease patient without expiratory flow limitation

of EFL. In our study, a negative but not statistically significant correlation was found. The presence of the relationship between IC and EFL in COPD patients shows the importance of NEP method in the determination of DH. It reveals the widespread use of NEP, which is an inexpensive, practical and easy to use method for the detection of DH in COPD patients. In our study, TLC, FRC, VC and RV values in both mL and % predicted values were correlated with IC as in the study by Diaz et al. (17).

CONCLUSION

In conclusion, we demonstrated that the examination of EFL by NEP method in COPD patients did not provide additional information about DH. We can say that IC is the best predictor of DH.

Ethics

Ethics Committee Approval: The study was approved by Ethics Board of İstanbul University Cerrahpaşa Faculty of Medicine, Department of Chest Disesase (approval no: 1724-2004).

Informed Consent: Informed consent has been taken from all the patients.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Concept: H.İ., Design: H.İ., Data Collection or Processing: H.İ., Analysis or Interpretation: H.İ., Literature Search: H.İ., Writing: H.İ., G.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Global Initiative For Chronic Obstructive Lung Disease. Global Strategy For The Diagnosis, Management, And Prevention of Chronic Obstructive Pulmonary Disease NHLBI/WHO Workshop Report. U.S. Department of Health and Human Services. Public Health service. National Institutes of Health. National Heart, Lung, and Blood Institute. NIH Publication No. 2701. April 2001.
2. Corne S, Anthonisen NR. Lung-function testing in chronic obstructive pulmonary disease. In: Voelkel NF, MacNee W editors. Chronic obstructive lung disease. Hamilton, BC Decker Inc. 2002:257-69.
3. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation and endurance during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;158:1557-65.
4. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation and endurance during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997;155.
5. Milic-Emil J. Expiratory flow limitation. Chest 2000;117:2195-235.
6. Baydur A, Milic-Emili J. Expiratory flow limitation during spontaneous breathing: comparison of patients with restrictive and obstructive respiratory disorders. Chest 1997;112:1017-23.
7. Murariu C, Ghezzo H, Milic-Emili J, Gautier H. Exercise limitation in obstructive lung disease. Chest 1998;114:965-8.
8. American Thoracic Society: Standardization of spirometry-1994 update. Am J Respir Crit Care Med 1995;152:1107-36.
9. Koulouris NG. Negative expiratory pressure: a new tool. Monaldi Arch Chest Dis 2002;57:69-75.
10. O'Donnell DE, Revill SM, A Webb K. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164:770-7.
11. O'Donnell DE. Assessment of bronchodilator efficacy in symptomatic COPD: is spirometry useful? Chest 2000;117:42-7.
12. Koulouris NG, Dimopoulou I, Valta P, Finkelstein R, Cosio MG, Milic-Emili J. Detection of expiratory flow limitation during exercise in COPD patients. J Appl Physiol 1997;82:723-31.
13. Eltayara L, Becklake MR, Volta CA, Milic-Emili J. Relationship between choronic dyspnea and expiratory flow limitation in patients with choronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996;154:1726-34.
14. Diaz O, Villafranca C, Ghezzo H, Borzone G, Leiva A, Milic-Emil J, et al. Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. Eur Respir J 2000;16:269-275.
15. Tantucci C, Duguet A, Similowski T, Zelter M, Derenne JP, Milic-Emili J. Effect of salbutamol on dynamic hyperinflation in choronic obstructive pulmonary disease patients. Eur Respir J 1998;12:799-804.
16. Koulouris NG, Valta P, Lavoie A, Corbeil C, Chassé M, Braidy J, et al. A simple method to detect expiratory flow limitation during spontaneous breathing. Eur Respir J 1995;8:306-13.
17. Diaz O, Villafranca C, Ghezzo H, Borzone G, Leiva A, Milic-Emil J, Lisboa C, et al. Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. Eur Respir J 2000;16:269-75.
18. Boni E, Corda L, Franchini D, Chiroli P, Damiani GP, Pini L. Volume effect and exertional dyspnea after bronchodilator in patients with COPD with and without expiratory flow limitation at rest. Thorax 2002;57:528-32.

ORIGINAL ARTICLE

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Personality Profile of Patients with Vocal Cord Nodules

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Abstract

Objective: We aimed to evaluate the susceptibility of patients with vocal cord nodules to psychoticism, extraversion, or neuroticism from the normal healthy population using the Eysenck's Personality inventory.

Methods: A study cohort consisting of patients followed up with vocal cord nodules and age- and gender-matched healthy controls was asked to answer the questions in the Eysenck's Personality inventory in a quiet and calm environment. The data were then evaluated and scored by the clinical psychologist, and personality profiles were determined.

Results: Eighty-six subjects (43 patients-43 controls) were included in the study. There was no significant difference between the groups in terms of mean scores of psychoticism (p=0.88) and extraversion (p=0.376), whereas the mean scores of neuroticism (p=0.027) and lie (p<0.01) were significantly different.

Conclusion: Although it is frequently encountered in daily practice, the personality characteristics of patients with vocal cord nodules are easily missed. However, determining this condition and therapy in this area may positively affect the treatment of the disease and may help to establish appropriate behavioral patterns to prevent recurrence.

Keywords: Vocal cord nodules, Eysenck's Personality inventory, psychotism

INTRODUCTION

Vocal cord nodules are seen at the junction of the middle 1/3 and the anterior 1/3 of the vocal cords. They usually occur as a result of excessive vibratory vocal trauma on the vocal cords (1,2). As a result of vibratory trauma, superficial lamina propria is disrupted and collagen 4 and fibronectin accumulate in this area (2). As a result of this accumulation, the vocal cords cannot be completely closed in the midline and laryngostroboscopy shows a typical hourglass view. Vocal cord nodules are seen in 0.5 to 1.3% of the general population (3). This disease is more common in people who use their voice for work, such as singers or teachers. It has been shown that most of the cases with vocal cord nodules tend to overuse their voices due to personality characteristics (4). Differences or tendencies in individuals' responses, such as thoughts, behaviors and emotions, which cannot be explained according to their situation, time or environment, can be defined as personality profile (5). Therefore, personality includes subjective and fixed features of the individual. Most of the authors think that because of these features, personality includes all aspects of the person from gestures and walks to speech and thinking (6). Many personality theorists have conceptualized personality in different ways. In the definition of personality, Eysenk used introversion and extroversion (E) dimension as the basis. He has created a three-dimensional structure by adding psychoticism (P) to the personality, which he had previously thought of as neuroticism (N) and E . E dimension shows social behaviors and impulsivity, N dimension shows emotional and overreactive behaviors, and P dimension shows distancing from people (7). In some previous studies, it has been found that features such as impulsivity and hyperactivity are more common in people with voice nodules (1,8,9). At the same time, it is noteworthy that patients with vocal cord nodules exhibit E characteristics and make statements about this. In this study, we aimed to evaluate the susceptibility to P, E, or N of patients with vocal cord nodules by Eysenck's Personality inventory (EPQ) and to evaluate the difference from normal healthy population.

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METHODS

The study was started with the approval of the ethics committee of İstanbul Gaziosmanpaşa Taksim Training and Research hospital (78/2018). The patients who were followed up with vocal cord nodule in the otorhinolaryngology clinic of our hospital and who were older than 18 years were asked to answer EPQ that consists of 101 questions in a quiet and calm environment. The control group included age- and gender-matched patients with no disease in the vocal cords. The data were then evaluated and scored by a clinical psychologist and personality profiles were determined.

Statistical Analysis

Normality of data was assessed using Shapiro-Wilk test, histogram, Q-Q plot and box plot graphs. Independent t-test was used to compare patient and control groups, as the data showed normal distribution. The level of significance was taken as $p<0.05$ with a two-tailed test. Analysis was performed using NCSS 10 (Kaysville, Utah, USA).

RESULTS

Forty-three patients and 43 age and gender-matched healthy subjects were included in the study. In each group, there were 37 female and six male subjects. The mean age of the patient group was 31.67±10.38 years and 31.88±10.2 years in the control group. The mean P score was 3.58±1.82 in the patient group and 4.27±1.91 in the control group. The mean score of E was 13.30±3.96 in the patient group and 12.51±4.27 in the control group (Figure 1). The mean score of N was 15.11±4.04 in the patient group and 13.04±4.49 in the control group. This result was found to be statistically different (p=0.027) (Figure 2). Lie subscale scores were scored as 15.23±2.61 in the patient group and 12.81±3.34 in the control group. The total score of the lie subscale was significantly higher in the patient group compared to the control group (p<0.001) (Table 1).

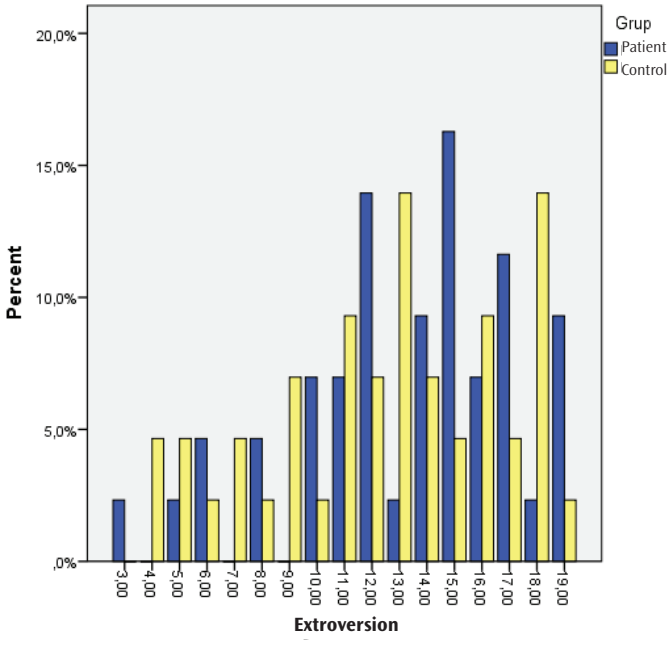

Figure 1. Extroversion scores of the patient and control groups

DISCUSSION

Vocal cord nodules, cysts and polyps, which are called benign vocal cord lesions, usually occur as a result of one or more repeated phonotrauma (2,10). In recent years, psychogenic factors and stress have been implicated in the development

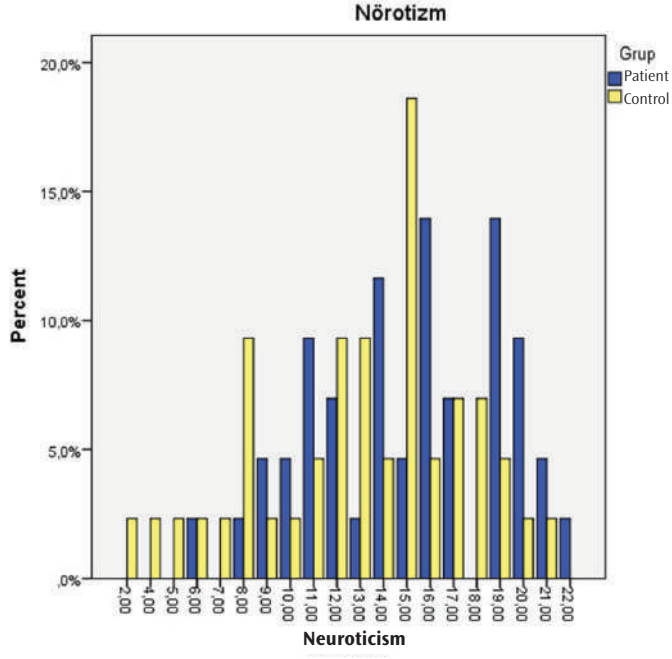

Figure 2. Neuroticism scores of the patient and control groups

Table 1. Distribution of the scores obtained in the inventory by groups and statistical results

Statistics					
	Group	**n**	**Mean**	**Standard deviation**	**p**
Psychoticism	Patient	43	3.5814	1.82877	0.88
	Control	43	4.2791	1.91890	
Extroversion	Patient	43	13.3023	3.96734	0.376
	Control	43	12.5116	4.27268	
Neuroticism	Patient	43	15.1163	4.04268	0.027
	Control	43	13.0465	4.49313	
Lie	Patient	43	15.2326	2.61713	<0.01
	Control	43	12.8140	3.34704	

of benign vocal cord lesions like many other diseases. It has been reported in some studies that stress affects sound quality (11) and causes acoustic changes (12-14). Smith and Seidel (15) reported that stress might cause voice problems (voice unsteady, strained, tense, loud, quiet) that would prevent communication in patients. In this study, the responses of the patients with vocal cord nodules to the EPQ were examined and the personality profile of the patients was investigated. The results were also compared with the normal population and their differences were evaluated. EPQ is one of the inventories that are frequently used in the outpatient clinic to evaluate introversion and E of individuals, and considered to be reliable due to its consistent results. The inventory was developed primarily to assess the normal characteristics of the individual, rather than the diseased conditions (10). According to H.J. Eysenck and S.B.G. Eysenck, the personality of the individual can be evaluated as a three-dimensional structure. These three dimensions are P, N and E. In order to evaluate the personality of the individual, they have worked on many inventories, and EPQ took its final form. EPQ is an inventory of 101 questions, 90 original and 11 substitute, for the purpose of evaluating four personality characteristics: P, E, N and lie. Twenty-three of these questions can be used to evaluate N, 21 for E, 25 for P, and 21 for lie. The individual is asked to answer "yes" and "no" to each question while completing this questionnaire (10). In this study, the N and lie values of our patients were higher than the control group and this difference was found to be statistically significant. According to these results, it can be said that the patient group is more anxious and more susceptible to stress than the control group. Moreover, the high lie score of the patient group may indicate that they do not feel socially sufficient and need to show themselves better. In a similar study, Barakah et al. (16) found that psychogenic factors were associated with benign vocal cord lesions, particularly in the formation of nodules, polyps, and cysts. Although the personality characteristics of patients with vocal cord nodules are observed in daily practice, not enough studies have been conducted. The effects of psychological characteristics on otolaryngology are the areas that have been studied more recently. In a limited number of previous studies, it was shown that personality characteristics were related to vocal cord nodule formation. In our study, we also found that E and N were more prominent in patients with vocal cord nodules.

Study Limitations

The limited number of patients and the fact that the psychiatric features of the patients such as depression and anxiety were not excluded are the limitations of our study.

CONCLUSION

In our study, it was found that individuals with vocal cord nodules had more neurotic features than the control group. Although this shows that patients cannot use the right defense mechanisms to cope with stress, it can be accepted that somatic symptoms are common in the patient group. Although it is common in daily practice, the personality characteristics of patients with vocal cord nodules are easily missed. However, determining this condition and therapy in this area may positively affect the treatment of the disease and may help to establish appropriate behavioral patterns to prevent recurrence.

Ethics

Ethics Committee: The study was reviewed by the ethics committee of İstanbul Gaziosmanpaşa Taksim Training and Research Hospital and it was found that there was no ethical problem in its publication (78/2018).

Informed Consent: Obtained from all patients.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.P., Concept: C.P., Design: C.P., H.S.Ş., Data Collection or Processing: C.P., Analysis or Interpretation: H.S.Ş., Literature Search: C.P., H.S.Ş., Writing: C.P., H.S.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. El Uali Abeida M, Fernández Liesa R, Vallés Varela H, García Campayo J, Rueda Gormedino P, Ortiz García A. Study of the influence of psychological factors in the etiology of vocal nodules in women. J Voice 2013;27:129.e15.
2. Dikkers FG, Nikkels PG. Benign lesions of the vocal folds: histopathology and phonotrauma. Ann Otol Rhinol Laryngol 1995;104:698-703.
3. Nagata K, Kurita S, Yasumoto S, Maeda T, Kawasaki H, Hirano M. Vocal fold polyps and nodules. A 10-year review of 1,156 patients. Auris Nasus Larynx 1983;10:27-35.
4. Bastian RW, Thomas JP. Do talkativeness and vocal loudness correlate with laryngeal pathology? A study of the vocal overdoer/underdoer continuum. J Voice 2016;30:557-62.
5. Linda V. Berens. Sixteen personality types: Descriptions for self-discovery. Telos Publications, California, 1999.
6. Taymur İ, Türkçapar M.H. Kişilik: Tanımı, sınıflaması ve değerlendirmesi psikiyatride güncel yaklaşımlar-current approaches in psychiatry 2012;4:154-77.

7. Eysenck HJ, Eysenck SBG. Manual of the eysenck personality questionnaire (adult and junior). London, Hodder & Stoughton, 1975. Personality: Description, Classification and Evaluation
8. Yano J, Ichimura K, Hoshino T, Nozue M. Personality factors in pathogenesis of polyps and nodules of vocal cords. Auris Nasus Larynx 1982;9:105-10.
9. Ratajczak J, Grzywacz K, Wojdas A, Rapiejko P, Jurkiewicz D. Role of psychological factors in pathogenesis of disturbances of voice caused with vocal nodules. Otolaryngol Pol 2008;62:758-63.
10. Eysenck SBG. The validity of a personality questionnaire as determined by the method of nominated groups. Life Sciences 1962;1:13-8.
11. Mossallam I, Kotby MN, Ghaly AF, Nassar AM, Barakah MA. Histopathological aspects of benign vocal fold lesions associated with dysphonia. In: Vocal Fold Histopathology San Diego: College-Hill Press 1986;65-80.
12. Everly GS, Lating JM. A Clinical guide to the treatment of human stress response. 2nd ed. New York, NY: Kluwer Academic Publischers; 2002.
13. Mendoza E, Caballo G. Acoustic analysis of induced vocal stress by means of cognitive workload tasks. J Voice 1998;12:263-73.
14. Mendoza E, Caballo G. Vocal tremor and psychological stress. J Voice 1999;13:105-12.
15. Smith JC, Seidel JM. The factor structure of self-reported physical stress reactions. Biofeedback Self-Regulation 1982;7:35-47.
16. Barakah MA, Mohammed MM, Shab YAA, Hegazi MA, Shoeib RM, Quriba AS. Psychogenic background of minimal associated pathological lesions of the vocal folds. Egyptian Journal of Ear, Nose, Throat and Allied Sciences 2012;13:55-9.

ORIGINAL ARTICLE

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Diagnostic and Prognostic Value of Neutrophil Lymphocyte Ratio in Patients with Acute Pancreatitis

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Abstract

Objective: Acute pancreatitis is an inflammatory disease of the pancreas with local and systemic complications, and high mortality and morbidity. A variety of scoring systems have been developed for the early detection of severe acute pancreatitis. However, they are not feasible enough to detect severe patients in the early period. This study aimed to investigate the relationship between neutrophil lymphocyte ratio (NLR) and etiology of acute pancreatitis, clinical presentation, early diagnosis of severe pancreatitis, length of hospital stay and complications.

Methods: A total of 150 patients with acute pancreatitis and 36 age and gender matched healthy controls were included. NLR was calculated within the first 24 hours of admission to the hospital. The results were compared with disease etiology, activity indices, complications, and length of hospital stay.

Results: In patients with acute pancreatitis, NLR levels (7.0±9.3) were found to be significantly higher than in the control group (1.8±0.6) ($p<0.05$). There was no statistically significant difference between biliary and non-biliary pancreatitis groups in terms of neutrophil, lymphocyte, NLR, CRP and sedimentation levels ($p>0.05$). Regarding Ranson's criteria and Modified Glasgow Prognostic score, NLR was significantly higher in patients with severe pancreatitis ($p<0.05$). However, there was no similar correlation with Balthazar score.

Conclusion: NLR was shown to increase in patients with acute pancreatitis as well as in other inflammatory conditions. NLR may be useful as an easily applicable parameter in the early diagnosis of disease and prediction of disease activity in patients with acute pancreatitis.

Keywords: Acute pancreatitis, neutrophil, lymphocyte, neutrophil lymphocyte ratio

INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas that develops when inactive pancreatic enzymes in the pancreatic parenchyma become active for various reasons or when the activated enzymes are not sufficiently inactivated (1). AP is an important disease that causes morbidity and mortality. The annual incidence ranges from 4.9 to 35 per 100.000 (2). In the United State, more than 300.000 patients are diagnosed with AP annually and approximately 20.000 patients die (3). Eighty percent of the cases are mild and recover without serious morbidity, but 20% have a severe course. There was no decrease in the frequency of severe pancreatitis over time (4). Different scoring systems have been developed to assess the severity of AP based on clinical and laboratory findings, radiological risk factors, severity grading systems, and various serum markers. Some of these scoring systems are used in the first hours of admission, while others are used in the first 48-72 hours or later. However, these predictive models have low specificity due to high false positive rates (5). Since the physiological response of circulating leukocytes to stress causes an increase in the number of neutrophils and a decrease in the number of lymphocytes, the ratio of these two subgroups is used as a marker of inflammation in inflammatory diseases (6). Severe AP is said to lead to poor prognosis, uncontrolled Systemic Inflammatory Response syndrome (SIRS) and Multiple Organ Dysfunction syndrome. White blood cell (WBC) count is one of the criteria for SIRS score in AP (7). The decreased number of lymphocytes associated with an increased number of neutrophils is associated with severe

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sepsis, bacteremia and surgical stress. Neutrophils trigger SIRS and inflammatory cascade, while lymphocytes decrease in severe sepsis. It has been associated with adverse outcomes in patients (6,8,9). The aim of this study was to investigate the relationship between neutrophil lymphocyte ratio (NLR) and etiology of AP, clinical presentation, early diagnosis of severe pancreatitis, length of hospital stay and complications.

METHODS

The study was approved by the Ethics Committee with decision no. 481, dated 17.05.2016.

The study included 150 patients who were older than 18 years, who had no history of malignant disease, and who were clinically and radiologically diagnosed with AP and hospitalized to the internal medicine clinic between 01.03.2014 and 01.04.2016. The files of the patients were scanned from the Hospital Information Management System. The results of radiological examinations were retrospectively analyzed in terms of age, gender, length of hospital stay, complete blood count, biochemistry, C-reactif protein (CRP) and sedimentation rate. We investigated the relationship between NLR in the first 24 hours after admission and etiology, as well as the relationship between NLR and clinical parameters [Ranson's criteria and Modified Glasgow Prognostic Score (mGPS)], inflammation parameters (CRP, sedimentation), radiological grading (Balthazar score) and length of hospital stay. The severity of pancreatitis was accepted as mild (0-3 points) and severe (4-11 points) according to Ranson's criteria. According to mGPS, score ≥3 was considered as severe pancreatitis (10,11). In the scales defined by Balthazar et al. (12) the grading was based on the degree of necrosis, the presence of inflammation and fluid collection. It was classified as mild (0-3 points), moderate (4-6 points) or severe (7-10 points) (12). Thirty six gender- and age-matched healthy individuals were included in the study as the control group.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0. In descriptive statistics, categorical data were expressed as number and percentage, and continuous data as mean, standard deviation, median, maximum and minimum. Normality tests were carried out using Kolmogorov-Smirnov test. The comparison of the continuous data from two independent groups was made using Independent Samples t-test if the assumptions of normality were met, and Mann-Whitney U test if not. Kruskall-Wallis test was used to compare continuous data in which a maximum of two independent groups were provided with the assumptions of non-normality. If differences were found between the groups, the difference is determined by adjusting the p values. Chi-square test was used to analyze categorical variables and Fisher's Exact test was used as the alternative when chi-square test conditions were not met. Spearman correlation was used for correlation analysis. The effect level and cut-off value were investigated by ROC curve.

RESULTS

A total of 150 patients with AP and 36 healthy individuals who met the inclusion criteria were included. Seventy-five AP patients (50%) were female and 75 (50%) were male. Of controls, 12 (33.3%) were male and 24 (66.7%) were female. The mean age of the patient group was 54.1±18.2 years and the mean age of the control group was 49.1±12.4 years. There was no statistically significant difference between the two groups in terms of age and gender ($p>0.05$, Table 1). The etiology of 150 AP cases was biliary in 41% (n=61) and non-biliary (alcohol, hypertriglyceridemia, drugs, autoimmunity, trauma, idiopathic) in 59% (n=89). The Ranson's criteria score at 48 hours was between 0-3 points (mild AP) in 121 patients (80.7%) and between 4-11 points (severe AP) in 29 patients (19.3%). According to mGPS within 48 hours after admission, 82% of the cases were evaluated as mild AP and 18% as severe AP. When the patient and control groups were compared in terms of neutrophil and lymphocyte levels in the first 24 hours after hospital admission, patient group had higher neutrophil levels and lower lymphocyte levels than the control group ($p<0.005$). The mean NLR was 7.0±9.3 in the patient group and 1.8±0.6 in the control group. NLR was significantly higher in the patient group than the control group ($p<0.05$, Table 1). The diagnostic value of NLR in distinguishing AP from the control group was investigated by plotting a ROC curve. It was found to

Table 1. Demographic characteristics and laboratory analysis of patients and controls

	Patients with acute pancreatitis	Healthy controls	p
Number of subjects	150	36	
Gender, female/male	75/75	12/24	0.072
Median age, years	50.0 (49.1±12.4)	55.0 (54.1±18.2)	0.120
Neutrophil	7.8 (8.6±4.8)	4.4 (4.4±1.0)	0.000
Lymphocyte	1.7 (1.8±1.0)	2.7 (2.6±0.7)	0.000
NLR	4.7 (7.0±9.3)	1.7 (1.8±0.6)	0.000
WBC (K/mm^3)	11.0 (11.6±5.2)	7.7 (8.0±1.9)	0.000
ESR (mm/S)	20.0 (29.1±27.8)	10.0 (9.7±2.3)	0.000
CRP (mg/L)	26.0 (70.9±100.0)	2.0 (2.6±2.0)	0.000

AP: Acute pancreatitis, WBC: White blood cells, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil-lymphocyte ratio

have 95% discriminatory power with an optimal threshold value of 3, sensitivity of 95.5% and specificity of 70% (Figure 1). When AP patients were evaluated in terms of etiology, mean NLR was 6.99±8.06 in biliary AP and 6.94±9.78 in non-biliary AP. There was no statistically significant difference between biliary and non-biliary AP in terms of NLR (p>0.05, Table 2). There was no statistically significant difference between biliary and non-biliary AP in terms of CRP, sedimentation, neutrophil and lymphocyte levels (p>0.005). According to the Ranson's criteria, mean NLR was 9.85±6.70 in patients with severe AP and 6.26±9.72 in patients with mild AP. NLR was significantly higher in cases with severe AP (p<0.01). According to mGPS, mean NLR was 11.79±10.31 in patients with severe AP and 5.90±8.76 in patents with mild AP. The difference between two groups was statistically significant (p<0.05). According to the Ranson's criteria and mGPS, CRP levels in patients with severe AP were significantly higher than those with mild AP (p=0.003 for Ranson's criteria and p<0.05 for mGPS). There was no difference between the groups in terms of sedimentation (p>0.005). According to Balthazar score, there was no statistically significant difference between NLR, sedimentation, neutrophil and lymphocyte levels (p>0.05). However, CRP was highest in severe AP.

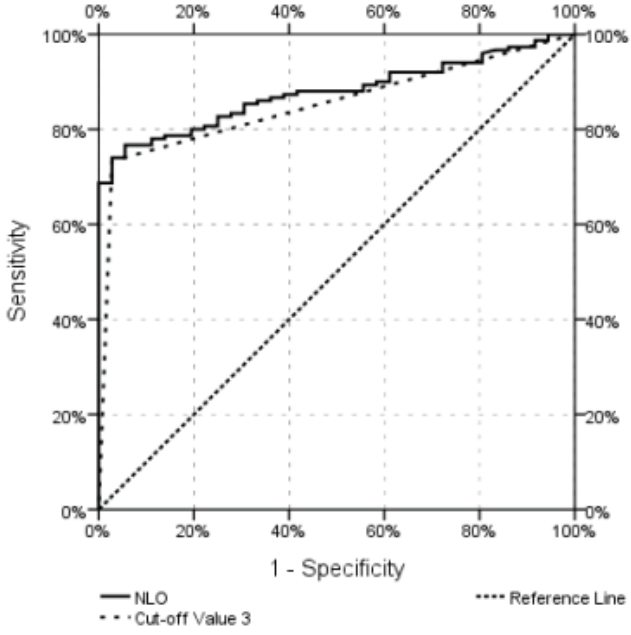

Figure 1. ROC curve analysis of neutrophil-lymphocyte ratio
NLO: Neutrophil-lymphocyte ratio

Table 2. Serum neutrophil-lymphocyte ratio levels in acute pancreatitis classified by potential categorical covariables

	n	NLR	p
Etiology			
Biliary	61	6.99±8.06	0.572
Non-biliary	89	6.94±9.78	
Ranson's criteria at 48 hours			
1-3; mild pancreatitis	121	6.26±9.72	<0.01*
4-11; severe pancreatitis	29	9.85±6.70	
Modified Glasgow Prognostic criteria (within 48 hours)			
<3; mild pancreatitis	123	5.90±8.76	<0.01*
≥3; severe pancreatitis	27	11.79±10.31	
Balthazar score			
0-3; mild pancreatitis	73	5.80±4.24	0.401
4-6; moderate pancreatitis	38	4.64±2.60	
7-10; severe pancreatitis	17	7.29±5.31	

NLR: Neutrophil lymphocyte ratio, *Statistically significant

When the correlation between NLR and sedimentation, CRP, neutrophil and lymphocyte parameters in patients with AP was investigated, NLR was found to have positive correlation with CRP and neutrophil levels (r=0.296, p<0.001; r=0.727, p<0.001, respectively) and negative correlation with lymphocyte levels (r=-0.625, p<0.001). There was no significant correlation between NLR and sedimentation (r=0.126, p>0.17). There was no statistically significant difference between complicated and non-complicated cases in terms of NLR (p>0.05). There was also no statistically significant correlation between NLR and length of hospital stay (p>0.05).

DISCUSSION

AP is an inflammatory disease of the pancreas with very different clinical features, ranging from transient abdominal symptoms to death (7). The incidence of AP has increased in many European and Scandinavian countries due to increased alcohol consumption and increased diagnostic methods (13). Since it is sometimes not recognized or diagnosed after death, the actual incidence is unknown. But the incidence of AP is assumed to be 5-35/100.000 (2). Recognition and evaluation of AP at an early stage is important in managing the treatment and avoiding recurrent episodes of pancreatitis. Gallstones and alcohol are the most common causes of AP. Other causes of AP include metabolic causes such as hyperlipidemia and hypercalcemia, surgical interventions, trauma, endoscopic retrograde cholangiopancreatography, infectious causes such as hepatitis B, cytomegalovirus and mycoplasma, some drugs, snake poisons or scorpion toxins (3). In our study, the etiology of AP was 41% biliary and 59% non-biliary (alcohol, hypertriglyceridemia, drugs, autoimmunity, trauma, idiopathic). In AP, there is still no easy, practical, inexpensive marker or parameter that will allow early diagnosis and give us an idea about the course and prognosis

of the disease. This study investigated whether NLR could be used as a parameter in the diagnosis, severity, progression and follow-up of AP. Leukocytes are markers of infection and inflammation, and are used in prognosis and follow-up in a majority of inflammatory diseases. They are also the part of many prognostic scoring systems for AP, including Ranson's criteria, Glaskow-Imrie and APACHE II (10,11,14).

Neutrophils are the most common type of leukocytes in the peripheral blood, which are produced from the stem cells in the bone marrow and then disseminated into circulation. Lymphocytes are specialized cells in the organism and carry various antigen receptors that recognize many foreign antigens. These receptors play an important role in response to these antigens and in the development of immune memory. Neutrophils spread inflammation and tissue destruction in AP through the activation of inflammatory cytokines [interleukin (IL)-6, IL-8 and tumor necrosis factor (TNF) alpha], a range of proteolytic enzymes (myeloperoxidase, elestase, collagenase) and free oxygen radicals. Lymphocytes increase following the initial stress, then fall within the first 24 hours and lymphopenia develops. Uncontrolled inflammation is considered to accelerate lymphopenia with accelerated apoptosis. Lymphopenia is associated with high mortality in patients with septic shock (8,9). Pezzilli et al. (15) reported lymphopenia in patients with AP that continued on day 1, followed by days 3 and 5 compared to other acute abdominal conditions and healthy controls. Consistent with the literature, this study found that patients with AP had a higher neutrophil level in the first 24 hours than the control group. However, lymphocyte level was significantly lower in AP group than in the control group (Table 1).

Nowadays, there are many studies in the literature showing the relationship between NLR and inflammation as well as various diseases. Some of the publications show that NLR can be used as an indicator of inflammation in various diseases such as ischemic stroke, atherosclerotic diseases, acute coronary syndrome and AP along with various types of cancer (16-19). Gibson et al. (20) stated that preoperative NLR accurately predicted the development of severe cholecystitis. Azab et al. (21) found that NLR increased in patients with AP. They also reported that NLR was superior to total WBC count or individual neutrophil and lymphocyte counts in predicting intensive care unit admission and mortality for AP. Our study supports the study by Azab et al. (21) and NLR was found to be significantly higher in AP group than in the control group. When the etiologic causes of AP were divided into two groups as biliary and non-biliary, there was no statistically significant difference between two groups in terms of NLR in our study ($p>0.05$). In a study conducted by Kara et al. (22), NLR was found to be high in patients with AP. However, there was no statistically significant difference between non-biliary and biliary AP in terms of NLR. Suppiah et al. (16) reported that increased NLR in patients with AP could effectively differentiate between patients with mild and severe AP. In our study, NLR in the first 24 hours was significantly higher in patients with AP than in the control group. In addition, NLR in patients with mild and severe AP was significantly higher when stratified according to the Ranson's criteria and mGPS ($p<0.05$). In a study of patients with AP, NLR cut-off value for the severity of the disease was suggested to be above 4.7 (21). Our study found that a cut-off value of 3 for NLR had 95.5% sensitivity and 70% specificity for diagnosis of AP. In recent years, the focus has been on a wide variety of clinical parameters, single biochemical markers, scoring systems and imaging procedures for the prediction of severe AP. Gülen et al. (23) demonstrated that contrast-enhanced CT imaging might be effective in determining the diagnosis and prognosis of AP. CT results of the patients included in this study were also re-evaluated by a radiologist according to Balthazar score. However, there was no statistically significant difference in terms of NLR when the patients were classified according to Balthazar radiological criteria ($p>0.05$). CRP is an acute phase reactant produced by the liver in response to IL-1, IL-6 and TNF-α, and is a low-cost marker that can be widely used to assess the severity of AP (24). A study conducted to predict AP showed that the simultaneous evaluation of erythrocyte sedimentation rate (ESR) and CRP is more successful than evaluating both variables separately. ESR can predict severe AP with slightly lower performance than that of CRP (25). In this study, we evaluated the relationship between ESR and CRP value and AP. We found no statistically significant difference in CRP levels between patients with biliary and non-biliary AP. According to Ranson's criteria and mGPS, CRP levels were significantly higher in patients with severe pancreatitis than in patients with mild pancreatitis. When CRP levels were examined according to Balthazar score, there was a difference between the grades. CRP levels were significantly higher in severe pancreatitis than mild pancreatitis. In addition, there was a statistically significant positive correlation between NLR and CRP, and these findings support the use of NLR as an inflammation marker in conjunction with CRP. Gürleyik et al. (26) reported that clinically severe AP had a longer hospital stay than that of clinically mild cases. In our study, no significant difference was found between severe and mild cases in terms of length of hospital stay.

CONCLUSION

In conclusion, NLR elevation was higher in the patient group than in the control group. NLR level was high in patients with severe pancreatitis according to Ranson's criteria and mGPS, but no difference was found in patients with severe pancreatitis according to the Balthazar criteria that is based on CT scoring. From this point of view, NLR can be used to diagnose AP as it can be correlated with CRP, which is widely used in routine practice. It can also be considered as a practical test for the early prediction of severe pancreatitis according to the Ranson's criteria and mGPS.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul Okmeydanı Training and Research Hospital Ethics Committee (approval no: 481, 17.05.2016).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.G., M.A., Design: Y.G., J.M., Data Collection or Processing: J.M., Analysis or Interpretation: Y.G., J.M., M.A., Literature Search: J.M., Writing: J.M., Y.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Vege SS. Clinical mnifestations and diagnosis of acute pankreatitis. Up to date, 2017.
2. Vege SS, Yadav D, Chari ST. Pancreatitis. In: Talley NJ, Locke GR, Saito YA editors. GI epidemiology Malden, MA: Blackwell Publishing; 2007.
3. Cappell MS. Acute pancreatitis: etiology, clinical presentation, diagnosis, and therapy. Med Clin North Am 2008;92:889-923.
4. Lund H, Tønnesen H, Tønnesen MH, Olsen O. Long-term recurrence and death rates after acute pancreatitis. Scand J Gastroenterol 2006;41:234-8.
5. Windsor JA. Assessment of the severity of acute pancreatitis: no room for complacency. Pancreatology 2008;8:105-9.
6. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102:5-14.
7. Otsuki M, Takeda K, Matsuno S, Kihara Y, Koizumi M, Hirota M, et al. Criteria for the diagnosis and severity stratification of acute pancreatitis. World J Gastroenterol 2013;19:5798-805.
8. de Jager CP, van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Wever PC. Lymphocytopenia and neutrophillymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care 2010;14:R192.
9. Le Tulzo Y, Pangault C, Gacouin A, Guilloux V, Tribut O, Amiot L, et al. Early circulating lymphocyte apoptosis in human septic shock is associated with poor outcome. Shock 2002;18:487-94.
10. Corfield A, Cooper MJ, Williamson R, Mayer AD, McMahon M, Dickson AP, et al. Prediction of severity in acute pancreatitis: Prospective comparison of three prognostic indices. Lancet 1985;2:403-7.
11. Demmy TL, Burch JM, Feliciano DV, Mattox KL, Jordan GL Jr. Comparison of multipl parameter prognostics systems in acute pancreatitis. Am J Surg 1988;156:2-6.
12. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: value of CT in establishing prognosis. Radiology 1990;174:331-6.
13. Toouli J, Brooke-Smith M, Bassi C, Carr-Locke D, Telford J, Freeny P, et al. Guidelines for the management of acute pancreatitis. J Gastroenterol Hepatol 2002;Suppl:S15-39.
14. Knaus WA, Draper Ea, Wagner DP, Zimmeran JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
15. Pezzilli R, Billi P, Beltrandi E, Casadei Maldini M, Mancini R. Impaired lymphocyte proliferation in human acute pancreatitis. Digestion 1997;58:431-6.
16. Suppiah A, Malde D, Arab T, Hamed M, Allgar V, Smith AM, et al. The prognostic value of the neutrophil-lymphocyte ratio (NLR) in acutepancreatitis: identification of an optimal NLR. J Gastrointest Surg 2013;17:675-81.
17. Binnetoğlu E, Akbal E, Güneş F, Sen H. The prognostic Value of Neutrophil-lymphosyte Ratio in Acute Pancreatitis is Controversial.J Gastrointest Surg 2014;18:885.
18. Gökhan S, Özhasenekler A, Mansur Durgun H, Akil E, Ustündag M, Orak M. Neutrophil lymphocyte ratios in stroke subtypes and transient ischemic attack. Eur Rev Med Pharmacol Sci 2013;17:653-7.
19. Temiz A, Gazi E, Güngör Ö, Barutçu A, Altun B, Bekler A, et al. Platelet/lymphocyte ratio and risk of in-hospital mortality in patients with ST-elevated myocardial infarction. Med Sci Monit 2014;20:660-5.
20. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. Am Heart J 2007;154:995-1002.
21. Azab B, Jaglall N, Atallah JP, Lamet A, Raja-Surya V, Farah B, et al. Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. Pancreatology 2011;11:445-52.
22. Kara H, Doğru A, Değirmenci S. Bayır A. Ak A. Kafalı ME, et al. Diagnostic value of neutrophil-to-lymphocyte ratio in emergency department patients diagnosed with acute pancreatitis. Çukurova Med J 2016:41:55-60.
23. Gülen B, Sonmez E, Yaylaci S, Serinken M, Eken C, Dur A, et al. Effect of harmless acute pancreatitis score, red cell distribution width and neutrophil/lymphocyte ratio on the mortality of patients with nontraumatic acute pancreatitis at the emergency department. World J Emerg Med 2015;6:29-33.
24. Khanna AK, Meher S, Prakash S, Tıwary SK, Singh U, Srivastava A, et al. Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI Scores, IL-6, CRP, and Procalcitonin in Predicting Severity, Organ Failure, Pancreatic Necrosis, and Mortality in Acute Pancreatitis. HPB Surg 2013;1-10.
25. Lankisch PG, Weber-Dany B, Hebel K, Maisonneuve P, Lowenfels AB. The harmless acute pancreatitis score: a clinical algorithm for rapid initial stratification of nonsevere disease. Clin Gastroenterol Hepatol 2009;7:702-5.
26. Gürleyik G, Emir S, Kiliçoglu G, Arman A, Saglam A. Computed tomography severity index, APACHE II score, and serum CRP concentration for predicting the severity of acute pancreatitis. JOP 2005;6:562-7.

ORIGINAL ARTICLE

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Non-urothelial Bladder Cancers: Single Center Experience

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Abstract

Objective: Bladder cancers are classified into two groups as urothelial and non-urothelial cancer (NUBC). In this study, we investigated the clinicopathological features and treatment responses in patients with NUBC who were diagnosed and treated in our center.

Methods: The patients who were diagnosed and treated in our hospital between 2006 and 2017 were included in the study retrospectively. Patients with urothelial or mixed bladder cancers were excluded from the study.

Results: A total of 16 patients with NUBC were included in the study. Six patients had squamous cell carcinoma, six patients had small cell carcinoma and four patients had adenocarcinoma. Thirteen patients (81%) were male and three were female. Although there was no statistically significant difference between the groups in terms of localization of metastases (p=0.663), the most common site of metastasis was pelvic structures in squamous cell carcinoma group and multiple distant organ metastasis were observed in small cell carcinoma group. The median survival in squamous cell carcinoma, adenocarcinoma, and small cell carcinoma was 11±5.3, 12±10, and 2±1.8 months, respectively (logrank p=0.329).

Conclusion: There are no large prospective randomized clinical studies to guide treatment in NUBC. In the light of these results, we recommend that these patients should participate in prospective clinical studies.

Keywords: Squamous cell cancer, small cell cancer, bladder cancer, chemotherapy

INTRODUCTION

Bladder cancers are the most frequently detected cancers of the genitourinary system in men and women. Bladder cancers are divided into two groups as urothelial and non-urothelial cancer (NUBC). Although the pathogenesis of NUBC has not been clarified, the main reason is thought to be infection and inflammation leading to metaplasia of epithelial cells (1). NBUCs are rare and consist of a histologically heterogeneous group, so there is no clear treatment approach. Appropriate treatment approaches were investigated with retrospective studies and small-scale prospective studies. Cystectomy and lymph node dissection are recommended in patients with early-stage adenocarcinoma (AC), squamous cell carcinoma (SqCC) and NUBC associated with schistosomiasis (2). Best supportive care, chemotherapy (CT), and radiotherapy (RT) are the treatment options for metastatic and inoperable NUBCs. The studies about targeted therapy based on tumor-specific mutations are ongoing in this group (3). We investigated the factors in the pathogenesis of disease, clinicopathological features of patients and responses to treatments in patients with NUBC who were diagnosed and treated in our center.

METHODS

The patients who were diagnosed and treated in our hospital between 2006 and 2017 were included in this study retrospectively. Patients with urothelial or mixed bladder cancer and non-bladder cancer were excluded from the study. A total of 16 patients were included in the study. Ethics committee approval was granted for the study.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) 15.0 for Windows was used for statistical analysis. Descriptive statistics were given as mean, standard deviation, minimum and maximum for numerical variables, and as number and percentages for

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categorical variables. The ratios were compared using chi-square test. Monte Carlo simulation was used when conditions were not met. Survival analysis was performed using Kaplan Meier analysis. The statistical significance alpha level was accepted as $p<0.05$.

RESULTS

A total of 16 patients with NUBC, including six patients with SqCC, six patients with small cell carcinoma (SCC), and four patients with AC, were included in the study. Thirteen patients (81%) were male and three (19%) were female. The mean age was 62.5±10.6 years. There was no statistically significant difference between the groups regarding gender and age (p=0.744 and p=0.743, respectively). A statistically significant difference was detected between the Eastern Cooperative Oncology group (ECOG) performance scores (p=0.011). The ECOG performance score of three SCC patients (66.3%) was 3. The ECOG performance score of three SqCC patients (50%) was 3. There was no statistically significant difference between the groups in terms of smoking (p=0.141). Smoking was a predisposing factor in two patients (12.5%) and chronic urinary infection was a predisposing factor in one patient (6.3%). There was no significant difference between the groups in terms of grade and stages (p=0.236, p=0.109). Ten patients (62.5%) had stage 4 disease at diagnosis. Five SCC patients (83.3%) had stage 4 disease at diagnosis. The most common site of metastasis was pelvic structures in all patients. Although there was no statistically significant difference between the groups in terms of metastasis site (p=0.663), the most common site of metastasis was pelvic structures in the SqCC group, but patients with SCC had multiple distant organ metastasis. Four patients (25%) underwent radical surgery and received postoperative adjuvant therapy. Local RT was performed in 8 patients (50%). Five patients (31.2%) received platin (cisplatin or carboplatin) plus gemcitabine CT, 3 patients (18.9%) received platin (cisplatin or carboplatin) plus etoposide (PE), one patient (6.3%) received platin (cisplatin or carboplatin) plus 5-fluorouracil, one patient (6.3%) received etoposide alone and one patient (6.3%) received gemcitabine alone. Thirteen patients (81.3%) died during the follow-up (Table 1). The median overall survival (OS) was 10±4.6 months for all patients and the median OS was 11±5.3, 12±10 and 2±1.8 months for SqCC, AC, and SCC, respectively (Table 2). There was no statistically significant difference between the groups in terms of OS (logrank p=0.329) (Figure 1).

DISCUSSION

NUBCs are less than 5% of all bladder cancers. Approximately 90% of NUBCs are epithelial cancers that may include SqCC, AC, and SCC. Non-epithelial tumors include sarcoma, carcinoma, paraganglioma, melanoma, and lymphomas (1). Other histological forms of bladder cancer are frequently observed seen in NUBCs. More than one tumor type was detected in 44 patients (68%) in a series of 64 patients and urothelial carcinoma (UC) component was detected in 38 patients (58%) (4). Similarly, in another study, a total of 51 patients with SCC were included and it was reported that the rates of simultaneously detected UC, AC and SqCC were 70%, 8% and 10%, respectively (5). We did not include any patients with mixed histology in our study. Six patients with pure SqCC, four patients with pure AC and six patients with pure SCC were included in this study. Chronic urinary tract infections are associated with bladder cancer. Infection can contribute to the development of bladder cancer through multiple mechanisms. SqCCs account for 3-5% of bladder cancers in North America and Europe. SqCC is most frequently associated with squamous metaplasia and is detected in 16-28% of patients with leukoplakia (6). However, in tendemic regions for Schistosoma haematobium infection, SqCC accounts for 75% of bladder cancers. Other risk factors for SqCC are bladder stone, pelvic RT, history of intravesical Bacillus Calmette-Guerin treatment, long-term use of cyclophosphamide and smoking (1,7). In our study, five SqCC patients had smoking history and one patient had chronic urinary tract infection. The predisposing factors in our study were smoking in two patients (12.5%) and chronic urinary tract infection in one patient (6.3%). The optimal treatment of non-metastatic SqCC is surgery. Preoperative RT is an acceptable option for local advanced disease. In a study in a total of 1422 male patients with SqCC, it was reported that the 2-year all-cause mortality rates were 11% in stage 1 disease and 72% in stage 4 disease. SqCC histology was associated with poorer outcomes compared with urothelial bladder cancer, and local recurrence was most frequently detected in SqCC (8). In Phase 3 BC2001 study, researchers observed that simultaneous administration of fluorouracil and mitomycin C with RT improved the local control and survival in patients with muscle-invasive bladder cancer. However, only 2.7% of the patients were diagnosed with AC or SqCC in this study (9). Limited data suggested that SqCC was relatively more resistant to CT regimens used in metastatic UC (10). In our study, 3 patients (50%) with SqCC were stage 2. Only one patient (16.7%) underwent curative surgery and was administered adjuvant cisplatin + gemcitabine treatment. RT was given to 3 patients (50%) at the time of diagnosis. Three patients had metastatic disease at the time of diagnosis, and all received palliative CT (platin+gemcitabine). Four patients died at a median follow-up of 12.8 months (range, 10.5-33.2). The median OS in SqCC was 11 months. AC is lower than 2% of all bladder cancers in North America and Europe.

Table 1. Comparison of demographic data according to histological groups										
				SqCC		AC		SCC		
		n	%	n	%	n	%	n	%	p
Gender	Male	13	81.3	4	66.7	4	100.0	5	83.3	0.744
	Female	3	18.8	2	33.3	0	0.0	1	16.7	
Age (years)	Mean ± SD (min-max)	62.5±10.6 (43-81)		61.0±11.2 (52-80)		62±12.1 (43-70)		64±10.7 (49-81)		0.743
ECOG PS	0	2	12.5	0	0.0	0	0.0	2	33.3	**0.011**
	1	4	25.0	2	33.3	2	50.0	0	0.0	
	2	4	25.0	3	50.0	1	25.0	0	0.0	
	3	4	25.0	0	0.0	0	0.0	4	66.7	
	4	2	12.5	1	16.7	1	25.0	0	0.0	
Smoking	Yes	11	68.8	4	66.7	4	100.0	3	50.0	0.141
	No	5	31.3	2	33.3	0	0.0	3	50.0	
Predisposing factors	Chronic UTI	1	6.3	1	16.7	0	0.0	0	0.0	0.518
	Smoking	2	12.5	1	16.7	1	25.0	0	0.0	
	None	13	81.3	4	66.7	3	75.0	6	100.0	
Grade	2	8	50.0	4	66.7	3	75.0	1	16.7	0.236
	3	8	50.0	2	33.3	1	25.0	5	83.3	
TNM stage	2	4	25.0	3	50.0	0	0.0	1	16.7	0.109
	3	2	12.5	0	0.0	2	50.0	0	0.0	
	4	10	62.5	3	50.0	2	50.0	5	83.3	
Metastasis sites at diagnosis	Lymph node	1	10.0	0	0.0	0	0.0	1	20.0	**0.663**
	Pelvic structures	5	50	2	66.7	1	50.0	1	40.0	
	Bone	1	10.0	0	0.0	1	50.0	0	0.0	
	Lung	1	10.0	1	33.3	0	0.0	0	0.0	
	Multiple	2	20.0	0	0.0	0	0.0	2	40.0	
Radical surgery	No	12	75.0	5	83.3	2	50.0	5	83.3	0.470
	Yes	4	25.0	1	16.7	2	50.0	1	16.7	
Chemotherapy	Adjuvant at diagnosis	4	25.0	1	16.7	2	50.0	1	16.7	0.959
	Palliative at diagnosis	7	43.8	3	50	1	25.0	3	50.0	
	None	5	31.2	2	33.3	1	25.0	2	33.3	
RT	At diagnosis	8	50.0	3	50.0	3	75.0	2	33.3	**0.614**
	Relapse/progress	1	6.3	1	16.7	0	0.0	0	0.0	
	None	7	43.8	2	33.3	1	25.0	4	66.7	
Chemotherapy	Etoposide	1	6.3	0	0.0	0	0.0	1	16.7	**0.527**
	Platin + flourourasil	1	6.3	1	16.7	1	25.0	0	0.0	
	Platin + etoposide	3	18.9	0	0.0	0	0.0	3	52.2	
	Platin + gemcitabine	5	31.2	4	66.7	1	25.0	0	0.0	
	Gemcitabine	1	6.3	0	0.0	1	25.0	0	0.0	
Final status	Alive	3	18.8	2	33.3	0	0.0	1	16.7	0.738
	Dead	13	81.3	4	66.7	4	100.0	5	83.3	

AC: Adenocarcinoma, ECOG PS: Eastern Cooperative Oncology group performance status, UTI: Urinary tract infection, SCC: Small cell carcinoma, RT: Radiotherapy, SqCC: Squamous cell carcinoma, TNM: Tumor nodule metastasis, SD: Standard deviation, Min: Minimum, Max: Maximum

Glandular, colloidal, signet-ring and clear cell variants have been described. The signet-ring cell variant is associated with poor prognosis. Metastasis is more frequently detected in AC than SqCC. Unlike UC, local recurrence is more common than distant metastasis (11). Surgery is the optimal treatment for AC. Partial cystectomy may be an alternative to radical cystoprostatectomy in patients with urachal AC. Partial cystectomy is not recommended in patients with non-urachal AC. There is no available randomized study focused on neoadjuvant or adjuvant CT. The role of CT or RT is not clear in patients with local advanced or metastatic AC (12). In a study, it was found that postoperative RT was associated with longer relapse-free survival and smaller local recurrence rate, but with a higher rate of distant metastases (13). In another prospective study, male patients with advanced stage NUBC were included and 11 patients had AC histology. Patients received ifosfamide, paclitaxel and cisplatin. Response rate was 36% and the median OS was 25 months (14). In another retrospective study of 14 patients with AC, the response rate was 36% for regimen containing first-line cisplatin (15). In our study, there were two patients (50%) with stage 4 AC and two patients (50%) underwent curative surgery. In our study, adjuvant therapy was administered to one patient (25%) and palliative CT was administered to three patients (75%). Platin combined with fluorouracil and gemcitabine were used as CT regimens. During the follow-up, all patients died due to cancer. In our study, the median OS in AC patients was 12 months. Bladder associated SCC is a rare, aggressive and poorly differentiated neuroendocrine neoplasm that represents less than 1% of all bladder cancers. There is no available randomized clinical study to guide the treatment of bladder SCC. Unlike UC, the presence or absence of muscle invasion in SCC has no effect on the treatment decisions because there is a high possibility of metastasis regardless of the tumor stage in SCC (16). In a retrospective study, 48 patients underwent surgery after neoadjuvant CT, 47 patients underwent surgery, and then 21 of 47 patients were administered adjuvant CT. Mainly PE or ifosfamide + doxorubicin were used as neoadjuvant treatment regimen. The 5-year survival was significantly longer in patients who were treated with neoadjuvant CT (79% versus 20%). The benefit of adjuvant CT on survival could not be demonstrated (17). In a retrospective study with patients from Mayo Clinic between 1980 and 2005, the 5-year survival rate was found to be significantly higher in 18 patients who were given postoperative adjuvant CT compared to patients who were not given adjuvant CT (43% versus 20%; p=0.03) (18).

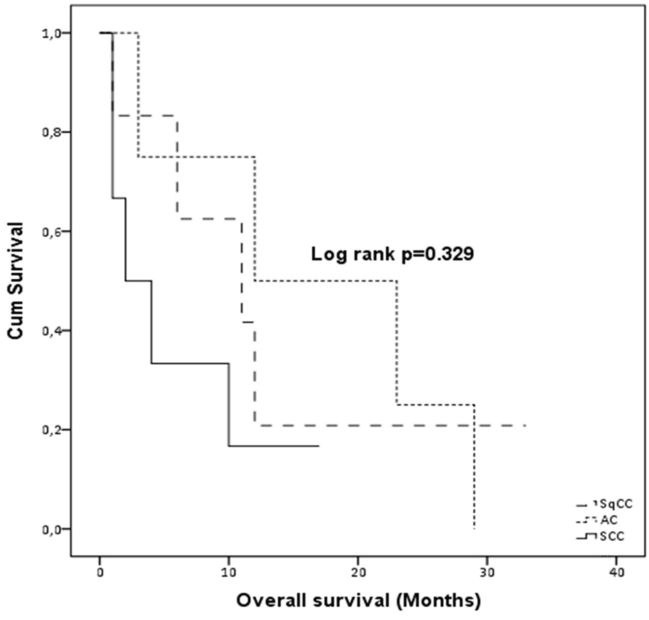

Figure 1. Survival according to histological groups
AC: Adenocarcinoma, SCC: Small cell carcinoma, SqCC: Squamous cell carcinoma

Table 2. The mean survival according to histological groups				
	Median (months)	SD	95% CI	
SqCC	11.0	5.3	0.5	21.4
Adenocarcinoma	12.0	10.0	0.2	31.6
SCC	2.0	1.8	0.5	5.6
All patients	10.0	4.6	0.8	19.1

SCC: Small cell carcinoma, SqCC: Squamous cell carcinoma, SD: Standard deviation, CI: Confidence interval

Higher response rates were detected in patients with metastatic bladder SCC treated with CT regimen that were used in lung SCC (19). The median OS in bladder SCC was approximately 7-13 months (19,20). Although systemic CT is the preferred treatment for metastatic disease, there is not enough data to guide the selection of the most appropriate regimen. In a prospective study, 12 patients with stage 4 disease (lymph node involvement was detected in only five patients) were treated with ifosfamide + doxorubicin, and PE, and complete response was obtained in three patients and surgical treatment could be performed. The median OS was found to be 13 months (19). In our presented study, there was one patient (16.7%) with stage 2 SCC and 5 patients (83.3%) with stage 4 SCC. One patient underwent curative surgery and received adjuvant PE. Two patients (33.3%) were administered local RT at the time of diagnosis. The median OS in SCC was detected as 2 months in our study. The reasons for shorter survival in SCC patients in the present study could be due to the detection of ECOG performance score as 3 in 4 patients (66.7%) and lack of CT in 2 patients due to lower ECOG performance.

CONCLUSION

In conclusion, there is no available large prospective randomized clinical study to guide the treatment in non-urothelial bladder cancer. Based on these results, we suggest that patients diagnosed with NUBC should be included in prospective clinical studies.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the İstanbul Okmeydanı Training and Research Hospital (approval no: 48670771-514.10).

Informed Consent: Patients were not required to give informed consent, because the study was retrospective and anonymous data were used, which were obtained after each patient agreed to treatment by written consent.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.S., N.Y., Concept: A.S., O.C., Design: A.S., S.A., O.C., Data Collection or Processing: A.S., N.Y., Ç.G., Analysis or Interpretation: S.A., Ş.S., C.D., Literature Search: C.D., N.Y., Ç.G., Writing: A.S., S.A., Ş.S.

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REFERENCES

1. Dahm P, Gschwend JE. Malignant non-urothelial neoplasms of the urinary bladder: a review. Eur Urol 2003;44:672-81.
2. Ghoneim MA, Ashamallah AK, Awaad HK, Whitmore WF Jr. Randomized trial of cystectomy with or without preoperative radiotherapy for carcinoma of the bilharzial bladder. J Urol 1985;134:266-8.
3. Loh KP, Mondo E, Hansen EA, Sievert L, Fung C, Sahasrabudhe DM, et al. Targeted Therapy Based on Tumor Genomic Analyses in Metastatic Urachal Carcinoma. Clin Genitourin Cancer 2016;14:e449-52.
4. Cheng L, Pan CX, Yang XJ, Lopez-Beltran A, MacLennan GT, Lin H, et al. Small cell carcinoma of the urinary bladder: a clinicopathologic analysis of 64 patients. Cancer 2004;101:957-62.
5. Choong NW, Quevedo JF, Kaur JS. Small cell carcinoma of the urinary bladder. The Mayo Clinic experience. Cancer 2005;103:1172-8.
6. Ozbey I, Aksoy Y, Polat O, Biçgi O, Demirel A. Squamous metaplasia of the bladder: findings in 14 patients and review of the literature. Int Urol Nephrol 1999;31:457-61.
7. Kantor AF, Hartge P, Hoover RN, Fraumeni JF Jr. Epidemiological characteristics of squamous cell carcinoma and adenocarcinoma of the bladder. Cancer Res 1988;48:3853-5.
8. Scosyrev E, Yao J, Messing E.Urothelial carcinoma versus squamous cell carcinoma of bladder: is survival different with stage adjustment? Urology 2009;73:822-7.
9. James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 2012;366:1477-88.
10. Serretta V, Pomara G, Piazza F, Gange E. Pure squamous cell carcinoma of the bladder in western countries. Report on 19 consecutive cases. Eur Urol 2000;37:85-9.
11. Grignon DJ, Ro JY, Ayala AG, Johnson DE, Ordóñez NG. Primary adenocarcinoma of the urinary bladder. A clinicopathologic analysis of 72 cases. Cancer 1991;67:2165-72.
12. Xiaoxu L, Jianhong L, Jinfeng W, Klotz LH. Bladder adenocarcinoma: 31 reported cases. Can J Urol 2001;8:1380-3.
13. Zaghloul MS, Nouh A, Nazmy M, Ramzy S, Zaghloul AS, Sedira MA, et al. Long-term results of primary adenocarcinoma of the urinary bladder: a report on 192 patients. Urol Oncol 2006;24:13-20.
14. Galsky MD, Iasonos A, Mironov S, Scattergood J, Donat SM, Bochner BH, et al. Prospective trial of ifosfamide, paclitaxel, and cisplatin in patients with advanced non-transitional cell carcinoma of the urothelial tract. Urology 2007;69:255-9.
15. Hong JY, Choi MK, Uhm JE, Park MJ, Lee J, Park SH, et al. Palliative chemotherapy for non-transitional cell carcinomas of the urothelial tract. Med Oncol 2009;26:186-92.
16. Patel SG, Stimson CJ, Zaid HB, Resnick MJ, Cookson MS, Barocas DA, et al. Locoregional small cell carcinoma of the bladder: clinical characteristics and treatment patterns. J Urol 2014;191:329-34.
17. Lynch SP, Shen Y, Kamat A, Grossman HB, Shah JB, Millikan RE, et al. Neoadjuvant chemotherapy in small cell urothelial cancer improves pathologic downstaging and long-term outcomes: results from a retrospective study at the MD Anderson Cancer Center. Eur Urol 2013;64:307-13.
18. Kaushik D, Frank I, Boorjian SA, Cheville JC, Eisenberg MS, Thapa P, et al. Long-term results of radical cystectomy and role of adjuvant chemotherapy for small cell carcinoma of the bladder. Int J Urol 2015;22:549-54.
19. Siefker-Radtke AO, Kamat AM, Grossman HB, Williams DL, Qiao W, Thall PF, et al. Phase II clinical trial of neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin in small-cell urothelial cancer. J Clin Oncol 2009;27:2592-7.
20. Ismaili N, Heudel PE, Elkarak F, Kaikani W, Bajard A, Ismaili M, et al. Outcome of recurrent and metastatic small cell carcinoma of the bladder. BMC Urol 2009;9:4.

ORIGINAL ARTICLE

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Evaluation of Echocardiographic Findings of Mucopolysaccharidosis Cases

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Abstract

Objective: Mucopolysaccharidosis (MPS) is a lysosomal storage disease in which the degradation of glycosaminoglycans is impaired. Cardiac involvement may occur in different ways in all types of the disease. In this study, we aimed to evaluate the echocardiographic reports of our patients with MPS retrospectively.

Methods: Echocardiography reports of 37 patients with MPS were reviewed retrospectively.

Results: Cardiac involvement was present in 70.2% our patients and the most commonly involved structure was mitral valve (59.5%). The most common pathology in mitral valve was mitral valve regurgitation (51.4%).

Conclusion: Cardiac involvement and complications are frequently seen in MPS. Heart failure, coronary artery involvement and arrhythmias are the main causes of death. Early diagnosis of MPS and early initiation of enzyme replacement therapy may improve cardiac involvement. Progressive valve involvement may require surgical intervention over time. For all these reasons, cardiac evaluation in MPS patients should be performed at least once a year with accompanying electrocardiogram and echocardiography.

Keywords: Mucopolysaccharidosis, echocardiography, cardiac involvement, mitral valve

INTRODUCTION

Mucopolysaccharidosis (MPS) are a group of lysosomal storage diseases characterized by chronic, progressive and multiple system involvement due to impaired glycosaminoglycans (GAG) degradation. There are 7 types of MPS as type I, II, III, IV, VI, VII and IX. MPS type III and IV are further sub-classified (1). There is wide clinical heterogeneity within this group of disorders, such as a dysmorphic features, learning difficulties, behavioral disturbance and bone dysplasia (2). Cardiac involvement can be seen in all types of MPS, and it is more common in MPS types I, II and VI, which have dermatan sulfate accumulation (3). Cardiac involvement may present with different presentations with the accumulation of GAGs in the cells of the endocardium, myocardium, valves, coronary arteries and transmission system. Cardiac findings, from asymptomatic valve involvement to severe heart failure, may be severe enough to cause mortality at an early age (3). The most common cardiac involvements in patients with MPS are thickening and deformity of the mitral and aortic valves, respectively (3). In this study, echocardiography reports of patients with MPS, who were diagnosed by enzymatic or genetic analysis, were examined and cardiac pathologies were evaluated according to MPS types.

METHODS

Patients diagnosed with MPS through enzymatic or genetic examinations in two centers were included in this study. Patients who did not attend follow up examinations in the last year or who did not undergo echocardiography in the last year were excluded from the study. Thirty-seven patients who fulfilled these conditions were included in the study and their files were reviewed retrospectively.

Statistical Analysis

All values were given as mean and standard deviation. Statistical

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analyzes were performed using SPSS 19 for Windows and Microsoft Excel 2017.

RESULTS

A total of 37 patients (15 female and 22 male) with MPS were included in the study. Four patients were MPS type 1, two were MPS type II, six were MPS type III, nine were MPS type IV and 16 were MPS type VI. The mean age of all patients was 99.9±67.5 months. Gender distribution and mean ages according to MPS types are given in Table 1. MPS type II patients with X chromosome transmission were male and had the lowest mean age. The highest mean age of the patients was in MPS type III.

All echocardiography reports of MPS patients included in the study were evaluated. Echocardiographic examination revealed cardiac pathology in 26 patients (70.2%). Echocardiographic examination of 11 patients (29.7%) was normal and the distribution according to MPS types is given in Table 1. The most common echocardiographic findings in type I MPS were mitral valve insufficiency and aortic valve insufficiency. Both type II MPS patients had mitral valve insufficiency. MPS type III patients had the least cardiac pathology, only one patient had bicuspid aortic valve and aortic valve insufficiency, and the remaining five patients had normal echocardiographic examination. The most common pathology in type IV MPS group was aortic valve insufficiency. The echocardiographic findings were most commonly observed in the MPS type VI group, and the most common pathology was mitral valve insufficiency (81.2%) and aortic valve insufficiency (37.5%) (Table 2). Regarding echocardiographic findings in all patients, 70.2% of the patients had cardiac involvement. It was seen that mitral valve was the most affected (59.5%) structure and the most common pathology was mitral valve insufficiency (51.4%). The second most common pathology was aortic valve insufficiency (32.4%). In addition, five patients had cardiomyopathy, three patients had bicuspid aortic valve and two patients had left ventricular hypertrophy.

Table 1. Gender, cardiac involvement and mean age distribution of patients according to mucopolysaccharidosis types

MPS	Female	Male	Negative cardiac involvement	Positive cardiac involvement	Age, months mean ± SD
Type 1	1	3	1	3	70.2±73.9
Type 2	0	2	0	2	47.5±12.0
Type 3	3	3	5	1	151.3±85.1
Type 4	3	6	4	5	95.8±69.2
Type 6	8	8	1	15	96.9±56.6
Total	15	22	11	26	99.9±67.5

SD: Standard deviation, MPS: Mucopolysaccharidosis

DISCUSSION

In MPS patients, accumulation of GAG in the endocardium and myocardium can cause cardiac involvement in all types. Cardiac findings vary from asymptomatic valve involvement to severe left ventricular failure and are a significant cause of mortality. Cardiac involvement is reported to be early and frequent in patients with MPS, especially in types I, II and IV (3,4). Thickening and loss of function of the heart valves (especially in the left heart) and hypertrophy are common, and coronary artery involvement or conduction disorders are rare (4). Electrocardiography and echocardiography are the key

Table 2. Echocardiographic findings of all mucopolysaccharidosis patients

Echocardiographic findings	MPS type I (n=4)	MPS type II (n=2)	MPS type III (n=6)	MPS type IV (n=9)	MPS type VI (n=16)	Total (n=37)
Mitral valve insufficiency	3 (75%)	2 (100%)		1 (11.1%)	13 (81.2%)	19 (51.4%)
Mitral valve prolapse	1 (25%)					1 (2.7%)
Mitral valve thickening				1 (11.1%)		1 (2.7%)
Mitral valve stenosis					1 (6.3%)	1 (2.7%)
Aortic valve insufficiency	2 (50%)		1 (16.7%)	3 (33.3%)	6 (37.5%)	12 (32.4%)
Aortic valve prolapse						-
Aortic valve thickening				1 (11.1%)		1 (2.7%)
Aortic valvestenosis						-
Bicuspid aortic valve			1 (16.7%)	1 (11.1%)	1 (6.3%)	3 (8.1%)
Left ventricular hypertrophy					2 (12.5%)	2 (5.4%)
Tricuspid valve insufficiency				1 (11.1%)	1 (6.3%)	2 (5.4%)
Cardiomyopathy	1 (25%)	1 (50%)			3 (18.8%)	5 (13.5%)

MPS: Mucopolysaccharidosis

tests to evaluate the cardiac involvement (4). However, it should be kept in mind that deformities (chest wall deformities) due to skeletal system involvement may cause difficulties during echocardiography examination in these patients. In our study, echocardiography reports of 37 MPS patients were examined. The reports of 11 patients were normal and 26 patients (70.2%) had cardiac involvement. The most frequent involvement was in the mitral valve (59.5%). The most common pathology was mitral valve insufficiency (51.4%), followed by aortic valve insufficiency (32.4%).

MPS type IV group had the highest cardiac involvement and MPS type III group had the lowest. In addition, five patients had cardiomyopathy, three patients had bicuspid aortic valve and two patients had left ventricular hypertrophy. In the literature, Mohan et al. (5) reported cardiac pathologies as mitral regurgitation (29%), aortic insufficiency (16%) and mitral stenosis (12%). It was also emphasized that mitral and aortic valve involvement increased with age (5). In 2010, 26 MPS patients were examined by Leal et al. (6) and the most common cardiac pathologies were mitral valve involvement (60%), left ventricular failure (43%), pulmonary hypertension (36%) and aortic valve involvement (35%). In the same study, it was reported that the most severe mitral involvement was in patients with MPS type VI (6). In our study, cardiac involvement was more common in MPS type VI patients, because the number of patients with MPS type VI was higher. In a study by Moog et al. (7) in 20 adult MPS type IIIB patients, one patient had mitral regurgitation, one patient had myocardial infarction, three patients had cardiomyopathy and four patients had atrial fibrillation. As a result of their study, cardiac involvement was reported to be low in MPS type III patients, but it was emphasized that cardiac examinations and investigations should not be neglected (7). In our study group, similarly, MPS type III patients had the least cardiac involvement. In the study of Braunlin et al. (8) it was reported that left ventricular hypertrophy improved in MPS type I patients after enzyme replacement therapy, but that mitral and aortic valve pathologies were not improved . In the study of Fesslová et al. (9) it was reported that cardiac functions might worsen immediately after bone marrow transplantation, but stabilization was achieved in long-term follow-up.

CONCLUSION

As a result, cardiac involvement and complications are frequently seen in MPS. Heart failure, coronary artery involvement and arrhythmias are the main causes of mortality. Early diagnosis of MPS and initiation of enzyme replacement therapy may improve cardiac involvement. In general, it should be noted that valve involvement may be progressive and may require surgical intervention over time. For all these reasons, cardiac evaluation should be performed regularly in MPS patients at least once a year, accompanied by electrocardiogram and echocardiography.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul Okmeydanı Training and Research Hospital Ethics Committee (approval number: 48670771-514.10).

Informed Consent: Informed consent from was patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.E.Ç., M.K., Concept: N.E.Ç., Design: N.E.Ç., Data Collection or Processing: N.E.Ç., M.K., Analysis or Interpretation: N.E.Ç., M.K., Literature Search: N.E.Ç., M.K., Writing: N.E.Ç., M.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Stapleton M, Arunkumar N, Kubaski F, Mason RW, Tadao O, Tomatsu S. Clinical presentation and diagnosis of mucopolysaccharidoses. Mol Genet Metab 2018;125:4-17.
2. Fernandes J, Saudubray J-M, Berghe G van den, Walter JH, editors. Inborn Metabolic Diseases: Diagnosis and Treatment. 4th ed. Berlin Heidelberg: Springer-Verlag 2006:580-3.
3. Dangel JH. Cardiovascular changes in children with mucopolysaccharide storage diseases and related disorders--clinical and echocardiographic findings in 64 patients. Eur J Pediatr 1998;157:534-8.
4. Braunlin EA, Harmatz PR, Scarpa M, Furlanetto B, Kampmann C, Loehr JP, et al. Cardiac disease in patients with mucopolysaccharidosis: presentation, diagnosis and management. J Inherit Metab Dis 2011;34:1183-97.
5. Mohan UR, Hay AA, Cleary MA, Wraith JE, Patel RG. Cardiovascular changes in children with mucopolysaccharide disorders. Acta Paediatr 2002;91:799-804.
6. Leal GN, de Paula AC, Leone C, Kim CA. Echocardiographic study of paediatric patients with mucopolysaccharidosis. Cardiol Young 2010;20:254-61.
7. Moog U, van Mierlo I, van Schrojenstein Lantman-de Valk HMJ, Spaapen L, Maaskant MA, Curfs LMG. Is Sanfilippo type B in your mind when you see adults with mental retardation and behavioral problems? Am J Med Genet C Semin Med Genet 2007 15;145:293-301.
8. Braunlin EA, Berry JM, Whitley CB. Cardiac findings after enzyme replacement therapy for mucopolysaccharidosis type I. Am J Cardiol 2006;98:416-8.
9. Fesslová V, Corti P, Sersale G, Rovelli A, Russo P, Mannarino S, et al. The natural course and the impact of therapies of cardiac involvement in the mucopolysaccharidoses. Cardiol Young 2009;19:170-8.

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Comparison of Efficacy of Intravitreal Aflibercept and Ranibizumab in Treatment-naive Diabetic Macular Edema

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Abstract

Objective: The purpose of this study was to compare the efficacy of two different intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents in two treatment-naive and statistically equal cohorts of diabetic macular edema patients.

Methods: In this retrospective study, 81 eyes of 64 treatment-naive diabetic macular edema (DME) patients were enrolled. Patients were divided into two groups and both groups were treated [37 eyes with intravitreal 0.5 mg ranibizumab (IVR) and 44 eyes with intravitreal 2 mg aflibercept (IVA)] with three consecutive injections at intervals of one month. All patients underwent a detailed eye examination including optic coherence tomography and best corrected visual acuity (BCVA; Snellen), biomicroscopy, fundoscopy and applanation tonometry at preoperative, 1st, 2nd and 3rd month. BCVA values were converted into logarithm of the minimum angle of resolution (logMAR) for statistical analyses. Data were evaluated with SPSS 25.0.

Results: Mean BCVA (logMAR) increased from 0.58±0.28 to 0.43±0.29, 0.39±0.25 and 0.32±0.26 ($p=0.001$, $p<0.001$, $p<0.001$) in the IVR group and from 0.54±0.28 to 0.41±0.34, 0.43±0.39 and to 0.32±0.37 ($p=0.004$, $p=0.023$, $p<0.001$) in the IVA group. Mean central macular thickness (CMT) decreased from 406±82 µm to 345±65 µm (1st month), 332±83 µm (2nd month) and finally to 303±60 µm (3rd month) ($p<0.001$) in the IVR group and from 415±88 µm to 328±79 µm, 297±54 µm and finally to 277±54 µm ($p<0.001$) in the IVA group, respectively. There was no significant difference between the groups in terms of BCVA ($p>0.05$). In the subgroup analysis, CMT gain in patients with moderate DME (CMT ≤385 µm) was found significantly better in the IVA group compared to the IVR group (1st month: 36.9 vs. 83.6, 2nd month: 36.2 vs. 106.3, 3rd month: 3nd 72.7 vs. 125.1; $p<0.05$).

Conclusion: Both anti-VEGFs were equally effective in visual outcomes. Compared to ranibizumab, aflibercept has a rapid and superior therapeutic effect in anatomical results, especially in moderate DME cases.

Keywords: Aflibercept, anti-vascular endothelial growth factor, diabetic macular edema, ranibizumab

INTRODUCTION

Diabetic macular edema (DME) is the most common cause of visual impairment in the diabetic population (1). According to a meta-analysis of 22.896 diabetic patients, the prevalence of center-involving DME was 6.81% (2). Historically, several interventional therapies such as focal/grid laser photocoagulation, intravitreal/periocular corticosteroids (triamcinolone acetonide etc.) or pars plana vitrectomy have proven to be effective in the treatment of focal or diffuse DME. However, intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) drugs with safe and effective profile have been considered as first-line therapy for DME in the last decade. Recently, the results of Protocol T trial of Diabetic Retinopathy Clinical Research Network (DRCR.net) - the most discussed comparison of three anti-VEGF drugs (ranibizumab, aflibercept on-label and bevacizumab off-label) - were published, including the post-hoc analysis in several publications (3,4). In this study, we aimed to compare the efficacy of two on-label anti-VEGFs in two comparable, treatment-naive diabetic edema cohorts under real-life conditions.

METHODS

This study was conducted at the İstanbul Okmeydanı Training and Research Hospital, Clinic of Ophthalmology. The study was approved by Clinical Research Ethics Committee of Okmeydanı Training and Research Hospital and adhered to the principles of the Declaration of Helsinki. Initially, medical records and

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electronic data of 121 eyes of 99 treatment-naive DME patients who underwent administration of three consecutive intravitreal anti-VEGF injections at a loading phase between August 2017 and November 2018 at our retina department were reviewed retrospectively. Our inclusion criteria were center-involving DME with a central macular thickness (CMT) >280 µm, proper administration of three consecutive monthly intravitreal anti-VEGF injections, availability of serum glycosylated hemoglobin A (HbA1C) levels in the peri-treatment period (±3 months at the initiation of the treatment), patients older than 18 years and diagnosis of type 2 diabetes mellitus (DM). Patients with type 1 DM, coexisting vitreoretinal interface pathologies such as epiretinal membrane, taut hyaloid or vitreomacular traction, any stage of proliferative diabetic retinopathy detected in baseline fluoresceine ongiography (FA), any intraocular surgery 6 months prior to the study, and ophthalmic comorbidities such as vein occlusion or glaucoma were excluded. According to our exclusion/inclusion criteria, 99 eyes of 82 patients were eligible for pre-enrollment evaluation. Further, we excluded 18 eyes of 18 patients from both intravitreal aflibercept (IVA) and intravitreal ranibizumab (IVR) groups to obtain statistically indifferent cohorts in terms of diabetes duration, serum HbA1C levels, gender distribution and age. Finally, 81 eyes of 64 patients were included in our retrospective study. All patients underwent a comprehensive ophthalmologic examination, including Snellen visual acuity testing, slit-lamp biomicroscopy, dilated fundus examination, Goldmann applanation tonometry, optical coherence tomography (OCT) examination with standard deviation-OCT (Spectralis; Heidelberg Engineering Inc, Heidelberg, Germany) by two certified technicians at all visits and FA at the pre-treatment period.

Statistical Analysis

Statistical analyses were performed using SPSS software version 25. The variables were investigated for normal distribution via visual (histogram) and analytical (Kolmogorov-Smirnov) methods. Visual acuities in Snellen (decimal) were converted to the logarithm of the minimum angle of resolution (logMAR) for statistical purposes. Independent t-test and Mann-Whitney U test were preferred to compare baseline demographical and clinical features between groups. Analysis were conducted in the entire study population and in two anatomical and visual subgroups of both treatment cohorts, based on baseline best corrected visual acuity BCVA levels and CMT values with the cut-off value of 0.3 Snellen lines and 385 µm. Repeated ANOVA measures was used to investigate the change in BCVA and CMT over time. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

A total of 81 eyes of 64 treatment-naive DME patients were included in the study. Forty-four eyes of 36 patients were taken into the IVA cohort and 37 eyes of 28 patients were taken into the IVR cohort. There was no significant difference between the groups in terms of age, gender, serum HbA1c levels, duration of diabetes, baseline BCVA and CMT values (Table 1). The IVR group was treated with of 0.5 mg IVR (Lucentis®, Genentech) for three consecutive months and the IVA cohort was given 2.0 mg IVA (EYLEA®, Regeneron Pharmaceuticals, Inc.) for three consecutive months.

Functional Outcome

Mean baseline BCVA (logMAR) improved in the IVR group from 0.58±0.28 to 0.43±0.29 (1st month, p=0.001), 0.39±0.25 (2nd month, p<0.001) and 0.32±0.26 (3rd month, p<0.001), respectively. In the IVA group, the mean BCVA also increased substantially from 0.54±0.28 to 0.41±0.34 (1st month, p=0.004), 0.43±0.39 (2nd month, p=0.023) and to 0.32±0.37 (3rd month, p<0.001). Regarding the total study population, the intergroup comparison between cohorts revealed no significant difference in monthly visits at follow-up (multivariate analysis, p=0.84) (Figure 1). In the subgroup analysis including eyes with low baseline BCVA (Snellen; VA <0.3), the intergroup comparison of IVR (n=18) and IVA (n=18) cohorts was insignificant at each visit (p=0.61) (Figure 2a). In the higher baseline BCVA (Snellen; VA ≥0.3) subgroup, although visual gain trends tended to be slightly superior in IVA cohort at the 1st month visit, statistical comparison of IVR (n=19) and IVA (n=26) cohorts revealed no significant difference (p=0.85) (Figure 2b).

Table 1. Baseline demographical and clinical features of both cohorts

	IVR (n=28*, n=37**)	IVA (n=36*, n=44**)	p
Age	61.9±7.9	58.3±9.2	0.07
Gender	M: 61.5%; F: 38.5%	M: 62.3%; F: 37.7%	0.94
Duration of DM (year)	11.2±2.3	12.3±2.2	0.64
HbA1c	7.38±0.5	7.34±0.6	0.75
PreCMT	406±82 µm	415±88 µm	0.62
PreBCVA (logMAR)	0.58±0.28	0.54±0.28	0.58

IVR: Intravitreal ranibizumab, IVA: Intravitreal aflibercept, M: Male, F: Female, DM: Diabetes mellitus, PreCMT: Pre-treatment central macular thickness; PreBCVA: Pre-treatment best corrected visual acuity, HbA1c: Glycosylated hemoglobin A, logMAR: Logarithm of the minimum angle of resolution
*Number of patients, **Number of study eyes

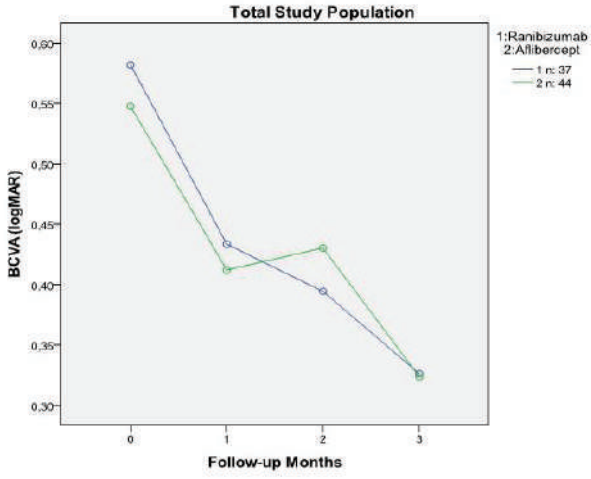

Figure 1. The visual gain comparison in the total study group
logMAR: Logarithm of the minimum angle of resolution, BCVA: Best corrected visual acuity

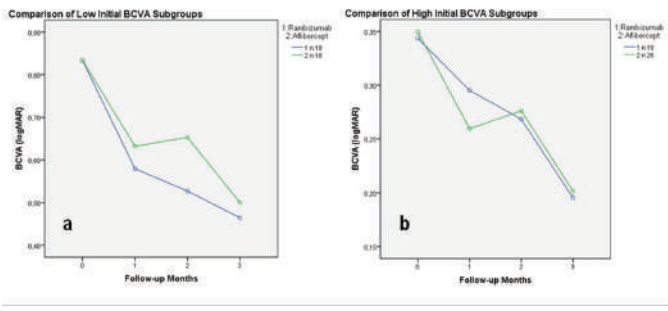

Figure 2. a) Comparison of intravitreal aflibercept and intravitreal ranibizumab groups in visual prognosis in low baseline best corrected visual acuity subgroup b) and in high baseline best corrected visual acuity subgroup
logMAR: Logarithm of the minimum angle of resolution, BCVA: Best corrected visual acuity

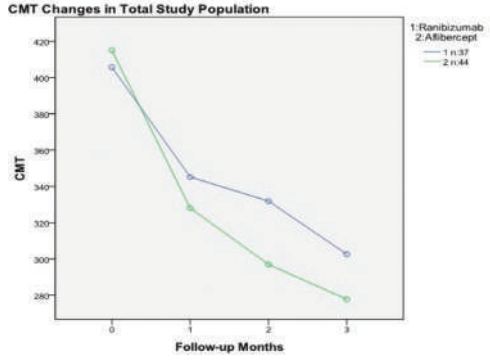

Figure 3. The regression of macular edema in the total study group
CMT: Central macular thickness

Anatomical Outcome

The mean CMT was significantly reduced in the IVR group from 406±82 µm to 345±65 µm (1st month), 332±83 µm (2nd month) and finally to 303±60 µm (3rd month) (p<0.001), respectively. In the IVA group, the baseline mean CMT also decreased significantly from 415±88 µm to 328±79 µm (1st month), 297±54 µm (2nd month) and finally to 277±54 µm (3rd month) (p<0.001), respectively. The intergroup comparison of monthly CMT values showed a significant superiority of IVA group at the 2nd month visit (p=0.03) (Figure 3). Additionally, the anatomical gain comparisons between IVR and IVA groups (60 vs. 87 µm; 73 vs. 118 µm; 103 vs. 137 µm) indicated a general superiority in the IVA group over IVR group, which was statistically significant at 2nd month visit (p=0.09; p=0.03; p=0.07, respectively). In the subgroup analysis of anatomical evaluation, we divided the total study group into severe and moderate DME subgroups according to the cut-off value (385 µm; median value). In severe DME (CMT >385 µm; IVR n=18; IVA n=22) cases, the mean CMT value in the IVR cohort decreased from 472±64 µm to 371±81 µm, to 340±94 µm and finally to 313±78 µm, respectively. In the IVA group, the mean CMT decreased from 483±74 µm to 362±92 µm, to 320±56 µm and finally to 291±61 µm, respectively. The intergroup comparison of CMT reduction in this severe DME subgroup revealed no significance (p=0.42) (Figure 4a). On the other hand, the mean CMT in IVR group with moderate DME decreased significantly from 343±28 µm to 321±32 µm, to 323±72 µm and finally to 292±34 µm at 3rd month visit (p<0.01). However, in the IVA group, a rapid and greater CMT reduction (from 346±24 µm to 294±45 µm, to 273±41 µm and to 264±45 µm; p<0.001) was observed. The comparison of both anti-VEGF agents in moderate DME cases revealed a statistically significant difference in favor of IVA group during the follow-up (p=0.03), starting from the 1st month visit (Figure 4b).

DISCUSSION

The major cause of visual loss in diabetic population with non-proliferative retinopathy is center-involving DME. The anti-VEGF drugs have dominated clinicians' treatment approach over the

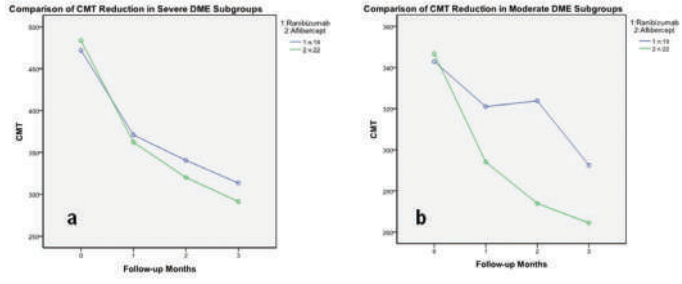

Figure 4. a) The subgroup analyses of central macular thickness reduction in response to intravitreal aflibercept and intravitreal ranibizumab treatments in severe macular edema cases b) and in moderate macular edema cases
CMT: Central macular thickness

last decade, with promising results and relative safety starting with the off-label use of bevacizumab (5). Following the usage of bevacizumab, two on-label agents, ranibizumab and aflibercept, were introduced into our daily practice with superior results from their representative trials (6,7). In addition, anti-VEGF agents have proved to be superior to conventional therapies. Monotherapy with IVR showed better clinical results than conventional laser photocoagulation (8). Corticosteroids such as dexamethasone has well-known potential risks such as cataract progression and glaucoma, so they have a limited indication in the treatment of DME patients (9). Therefore, clinicians prefer anti-VEGFs as the first-line therapy for this common clinical entity (10).

The on-going debate about which anti-VEGF would be recommended in each individual case has often been dependent on the clinician's experience in daily practice, local administrative regulations of the countries or financial issues. Recently, the comparative clinical trial Protocol T of DRCR.net reported first and second year results (3,4). While the overall visual results of the first year did not reveal any statistical difference between these three anti-VEGFs, aflibercept was significantly superior compared to ranibizumab (p=0.0003) and bevacizumab (p=0.0001) in the lower baseline BCVA (≤20/50) subgroup (3). Regarding the anatomical results of the whole study population, the greatest decrease in mean CMT was found in the aflibercept group (169±139 µm vs. 147±134 µm vs. 101±121 µm) at the end of the 1st year. However, for the 2nd year results of this trial, the ranibizumab group caught up on the aflibercept group both in visual and anatomical gains (12.8 letters vs. 12.3 letters; 171±141 µm vs. +149±141 µm), both on-label anti-VEGFs remained their superiority over bevacizumab (4). The Protocol T results partially supported the theoretical superiority aflibercept in visual gain, especially in low-vision cases. Therefore, we tried to compare ranibizumab and aflibercept in different baseline BCVA subgroups and aimed to find any differences in a particular clinical situation. Contrary to Protocol T findings in low baseline BCVA subgroup analysis, the IVA group in our study did not differ from the IVR group at any particular visit. Both anti-VEGF groups reached comparable functional endpoints at the final visit, such as the final result of the 2nd year of the Protocol T trial.

The reason for better efficacy of aflibercept over the 1st year results of the Protocol T trial may be due to its broader pharmacological features. In contrast to the antibody-based VEGF binding mechanism of ranibizumab and bevacizumab, aflibercept blocks the specific binding domains of the VEGF receptor (VEGFR)-1 and the VEGFR-2 (11). Aflibercept binds all isoforms of VEGF-A like the other two anti-VEGFs, additionally it also binds VEGF-B and placental growth factor, and the intermediate size of the molecule (110 kD, compared to 48 kD for ranibizumab and 148 kD for bevacizumab) create a potential monthly intravitreal activity that theoretically exceeds both ranibizumab and bevacizumab (12). This long-lasting effect is also reflected in some practical clinical reports. In their study comparing ranibizumab and aflibercept, Shimizu et al. (13) concluded that visual improvement in DME patients following consecutive intravitreal injections lasted significantly longer in aflibercept group than in ranibizumab group (6 vs. 3 months). In the IVA arm of their report, a subgroup of the patients had previous IVR treatment for DME. They found that IVA treatment did not improve the visual acuity further in previously treated IVR subgroup, but that the mean CMT decreased equally in both subgroups with or without prior IVR history. We believe this finding actually points to the additional anatomical efficacy of aflibercept. In the subgroup analysis of anatomical results of our study, IVA and IVR were found to be comparatively effective in the total study population, except for the 2nd month visit, and in the severe DME subgroup, but IVA proved to be significantly more effective in moderate DME cases. As a general rule, the more severe the macular edema, the more dramatically the CMT will decrease as a response to an effective treatment modality, however, the fact being significantly more effective in reducing the mean CMT of moderate DME cases clearly indicated the superior anatomical efficacy of aflibercept, probably due to its VEGF-trap character. The major limitations of this current study were clearly its retrospective nature and the absence of any randomization. We tried to eliminate the biases arising from its design by reviewing a large number of patient data and enrolling only eligible patients in the IVR and IVA groups to conduct two comparable treatment arms. Unlike representative clinical trials of anti-VEGFs (14,15), where patients get a much higher amount (7-12 times/year) of regular injections, real life based reports such as the Pride Study (16) reveal a much lesser frequency of intravitreal treatments (4 IVR injections/18 months). This fact clearly emphasizes the difference between randomized clinical trials and evidence findings in the real world.

CONCLUSION

In conclusion, our results demonstrated that ranibizumab and aflibercept were equally effective in visual prognoses of treatment-naive center-involving DME cases. Aflibercept distinguished itself in anatomical results, especially in moderate DME subgroups. The finding might be due to the multiple-sided inhibiting mechanism of aflibercept. Further real-world experience reports are needed for comprehensive evaluation of our conclusions.

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Ethics

Ethics Committee Approval: The ethics commitee approval was obtained from the local ethical commitee at İstanbul Okmeydanı Training and Research Hospital (approval number: 1116).

Informed Consent: Written informed consent was obtained from each participicant of this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.E., A.Ç., A.C.A., S.B., Concept: B.E., A.Ç., S.B., Design: B.E., A.Ç., M.N.E., Data Collection or Processing: A.C.A., B.E., S.B., A.Ç., Analysis or Interpretation: B.E., A.Ç., Literature Search: B.E., A.Ç., A.C.A., S.B., Writing: B.E., A.Ç., S.B.

Conflict of Interest: The authors of this study do not have any conflict of interest

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REFERENCES

1. O'Doherty M, Dooley I, Hickey-Dwyer M. Interventions for diabetic macular oedema: a systematic review of the literature. Br J Ophthalmol 2008;92:1581-90.
2. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556-64.
3. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015;372:1193-203.
4. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology 2016;123:1351-9.
5. Haritoglou C, Kook D, Neubauer A, Wolf A, Priglinger S, Strauss R, et al. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. Retina 2006;26:999-1005.
6. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119:789-801.
7. Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, et al. One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema. Ophthalmology 2012;119:1658-65.
8. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118:615-25.
9. Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, Augustin AJ, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology 2014;121:1904-14.
10. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, et al. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica 2017;237:185-222.
11. Holash J, Davis S, Papadopoulos N, Croll SD, Ho L, Russell M, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A 2002;99:11393-8.
12. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol 2008;92:667-8.
13. Shimizu N, Oshitari T, Tatsumi T, Takatsuna Y, Arai M, Sato E, et al. Comparisons of Efficacy of Intravitreal Aflibercept and Ranibizumab in Eyes with Diabetic Macular Edema. Biomed Res Int 2017;2017:1747108.
14. Brown DM, Schmidt-Erfurth U, Do DV, Holz FG, Boyer DS, Midena E, et al. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. Ophthalmology 2015;122:2044-52.
15. Ishibashi T, Li X, Koh A, Lai TY, Lee FL, Lee WK, et al. The REVEAL Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy in Asian Patients with Diabetic Macular Edema. Ophthalmology 2015;122:1402-15.
16. Menchini U, Bandello F, De Angelis V, Ricci F, Bonavia L, Viola F, et al. Ranibizumab for Visual Impairment due to Diabetic Macular Edema: Real-World Evidence in the Italian Population (PRIDE Study). J Ophthalmol 2015;2015:324841.

ORIGINAL ARTICLE

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Evaluation of Preschool Children with the Diagnosis of Non-epileptic Paroxysmal Disorders in a Pediatric Neurology Outpatient Clinic

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Abstract

Objective: Recurrent non-epileptic disorders that differ according to age play an important role in the differential diagnosis of childhood epilepsy. The aim of this study was to evaluate preschool children with recurrent non-epileptic paroxysmal disorders who were admitted to a pediatric neurology outpatient clinic.

Methods: Seventy-five children younger than 6 years of age who were admitted to a pediatric neurology outpatient clinic between January 2017 and January 2018 due to recurrent non-epileptic disorders were included in the study. The number of patients presenting with seizures and all other diagnoses were also recorded. Descriptive statistical analyses and chi-square test were used as statistical methods.

Results: Of the patients, 36 were female (48%) and 39 (52%) were male. The mean age was 22.5±17.2 months, with the youngest patient being 2 months and the oldest patient being 69 months old. Sixteen different diagnoses were detected. The prevalance of the disorder among 1575 new patients was 4.7%. The two most common diagnoses were breath-holding spells and gratification disorder. Of all patients, 29 patients (39%) had breath-holding spells and 46 (61%) had other diagnoses. Episode during examination happened most commonly in tic disorders, and least commonly in breath-holding spells and gratification disorder. The need for home video recording for diagnosis was mostly in patients with gratification disorder. Episode during examination, and need for video recording, sleep electroencephalography and cranial magnetic resonance imaging were significantly lower in breath-holding spells compared with other diagnoses ($p<0.05$). Children with the diagnoses of breath-holding spells was prescribed and used more iron formulations and piracetam than the patients with other non-epileptic paroxysmal disorders ($p<0.05$).

Conclusion: Home video recordings can prevent a misdiagnosis of epilepsy in patients with recurrent non-epileptic paroxysmal disorders. Accurate and timely diagnosis is possible without the need for further examination with medical history only in cases where the clinical symptoms are stereotypic.

Keywords: Differential diagnosis, epilepsy, preschool children

INTRODUCTION

Paroxysmal non-epileptic disorders of childhood are complex conditions involving recurrent intermittent motor movements, behavioral changes and somatic symptoms. These recurrent, sudden starting and ending movements that last seconds or minutes can occur at any age (1). The examples include sleep myoclonus for newborn age, breath-holding spells and gratification disorder for infants, and and tic and night terrors for preschool children. Epileptic seizures are quite common in the pediatric population, and the annual prevalence of epilepsy is around 0.5-1% (2). When paroxysmal disorders are encountered in childhood, epileptic seizures come to mind first. Therefore, patients with paroxysmal non-epileptic disorders are sometimes diagnosed with epilepsy and subjected to unnecessary investigations and treatment. In a retrospective study conducted in the UK, it was found that 44 (35%) out of 125 children who were referred with the diagnosis of epilepsy had no epilepsy (3). Accurate diagnosis may be delayed due to the presence of different disorders for each age group, limited facility for video electroencephalography (EEG) monitoring, and inadequate access to tertiary pediatric neurology centers. In a study from the United States, 134 children with paroxysmal non-epileptic disorders were evaluated and the time from onset of symptoms to diagnosis was found to be 1.35 years (3 weeks-4 years) (4). Increased knowledge and experience of paroxysmal non-epileptic disorders for each age group will prevent the misdiagnosis of epilepsy and therefore will reduce the use of antiepileptic drugs

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with high potential of side effects and ensure that patients are followed up with accurate diagnosis. The aim of this study was to evaluate the clinical and laboratory characteristics of infants and preschool children admitted to the pediatric neurology outpatient clinic with paroxysmal disorders, and diagnosed with paroxysmal non-epileptic disorder, and to investigate the prevalance of the disorder in the pediatric neurology outpatient clinic compared with seizures and epilepsies.

METHODS

Seventy-five children under 6 years of age who were admitted to the pediatric neurology outpatient clinic of Okmeydanı Training and Research Hospital between January 2017 and January 2018 due to paroxysmal non-epileptic disorders were included in the study. Patients with the diagnosis of syncope were not included in the study in terms of cardiologic etiologies in the differential diagnosis of syncope. The collected data were as follows: gender, age, duration of follow-up, complaints, duration of complaints, frequency of complaints, definitive diagnosis, episode during examination, need for video for diagnosis, request for sleep EEG, request for cranial magnetic resonance imaging (MRI), EEG results, cranial MRI results, antiepileptic use, whether there was a definitive diagnosis of epilepsy, neurological examination, laboratory test results, results of radiological and electrophysiological examinations, results of pediatric cardiology consultation and other departments included in the consultation, and iron and piracetam drug use. The families of the patients were asked to videotape the complaints in order to evaluate the disorders. The parents of the patients with missing data were contacted by phone and the missing data were completed, and data regarding the latest status of the patient, newly added diagnoses, episode status, and the changes in episodes were updated. However, five out of 75 patients could not be reached by phone. The frequency of the investigated disorder was also examined in our outpatient clinic by evaluating the number of patients under 6 years of age who were admitted to the pediatric neurology outpatient clinic for febrile seizures and epilepsy, and the number of new patients from the same age group admitted during this period.

Statistical Analysis

The analysis was performed using the Statistical Package for the Social Sciences 23 (SPSS, Armonk, NY: IBM Corp.). For numerical variables, mean, standard deviation, minimum and maximum values were given. For categorical variables, frequency distributions (number, percentage) were given. Independent Samples t-test was used to determine the difference between the

Table 1. Characteristics of all patients

Gender	n (%)		
Female	36 (48%)		
Male	39 (52%)		
Age group			
Infant	48 (64%)		
Preschool child	27 (52%)		
Complaint frequency			
Daily	42 (56%)		
Frequently	15 (20%)		
Occasionally	12 (16%)		
Rarely	6 (8%)		
Neurological examination			
Normal	71 (95%)		
Abnormal	4 (5%)		
Complaint	**n**	**Final diagnosis**	**n (%)**
Cyanosis while crying	29	Breath-holding spell	29 (38.7%)
Scissoring of lower extremities	12	Gratification disorder	12 (16%)
Waking up with fear from sleep at night	5	Night terror	5 (6.7%)
Suppressible involuntary movements	4	Tic disorder	4 (5.3%)
Jerking	4	Benign myoclonus of infancy	4 (5.3%)
Jerking	1	Hyperexplexia	1 (1.3%)
Throwing head back and sideways	4	Sandifer syndrome	4 (5.3%)
Head nodding	1	Head nodding	1 (1.3%)
Head nodding	2	Idiopathic infantile nystagmus	3 (4%)
Nystagmus and bending the neck	1		
Staring	3	Staring attack	3 (4%)
Nystagmus and bending the neck	1	Spasmus nutans	1 (1.3%)
Shuddering	2	Shuddering attack	2 (2.7%)
Nystagmus and dizziness	2	Benign paroxysmal vertigo	2 (2.7%)
Hand turning	1	Nonspecific paroxysmal non-epileptic disorder	2 (2.7%)
Hand flapping when excited	1		
Jerking in the legs	1	Jitteriness	1 (1.3%)
Cyanosis	1	Gastroesophageal reflux	1 (1.3%)

two groups. Chi-square test was used to examine the relationship between categorical variables and test results are given in tables.

RESULTS

Between January 2017 and January 2018, a total of 1575 new patients under the age of 6 were admitted to the pediatric neurology outpatient clinic and 485 (31%) of them were evaluated for febrile seizures and epilepsy. Paroxysmal non-epileptic disorder was considered in 75 patients (4.7%). Of the patients, 36 were female (48%) and 39 were male (52%). The mean age was 22.5±17.2 months and median age was 17 months. The youngest patient was 2 months old and the oldest one was 69 months old. Forty-eight patients (64%) were infants and 27 (36%) were preschool children. The duration of complaints was 7.44±9.23 months with a median of 5 months. The most common complaints were cyanosis while crying and scissoring of the lower limbs, and the first two diagnoses were breath-holding spells and gratification disorders. All of our breath-holding spells were cyanotic. The youngest patient was diagnosed with jitter and the oldest patient was diagnosed with tic disorder. Sixteen different diagnoses were determined and the least common diagnosis was gastroesophageal reflux. Table 1 presents demographic data, complaints, frequency of complaints, definitive diagnosis and neurological examinations of all patients. The definitive diagnoses of patients with hand-turning and hand flapping complaints when getting excited were classified as non-specific paroxysmal non-epileptic disorder. As breath-holding spells were the most common diagnosis, seventeen patients (35%) were infants and 12 patients (44%) were preschool children. Episodes during the examination were observed most frequently in patients with tic disorder and least frequently in patients with breath-holding spells and pediatric gratification disorders. The need for video for diagnosis was most commonly seen in patients with childhood gratification disorder, followed by infantile benign myoclonus and Sandifer syndrome (Table 2). Of all patients, 29 (39%) were diagnosed with breath-holding spells while remaining 46 (61%) were diagnosed with other etiologies. Episode rate, video request rate, sleep EEG request rate and cranial MRI request rate were found to be lower in patients diagnosed with breath-holding spells than those with other diagnoses ($p<0.05$) (Table 3). None of the patients diagnosed with breath-holding spells were requested for video for the diagnosis, three patients were requested for EEG and one patient for cranial MRI, and two patients admitted with EEG results requested from an external center and all were normal. Pediatric cardiology consultation was performed in 25 (86%) of 29 patients with breath-holding spells, and it was found that 15 patients (60%) had normal results, six patients (24%) had patent

Table 2. Distributions by diagnostic status

	Infant		Preschool		Episode during examination		No attack during examination		Video required for diagnosis		Video not required for diagnosis	
	n	%	n	%	n	%	n	%	n	%	n	%
Breath-holding spell	17	35.4	12	44.4	0	0.0	29	49.2	0	0.0	29	60.4
Head nodding	1	2.1	0	0.0	0	0.0	1	1.7	0	0.0	1	2.1
Benign myoclonus of infancy	4	8.3	0	0.0	1	6.3	3	5.1	3	11.1	1	2.1
Gratification disorder	11	22.9	1	3.7	0	0.0	12	20.3	12	44.4	0	0.0
Sandifer syndrome	4	8.3	0	0.0	2	12.5	2	3.4	3	11.1	1	2.1
Night terror	1	2.1	4	14.8	0	0.0	5	8.5	2	7.4	3	6.3
Spasmus nutans	1	2.1	0	0.0	1	6.3	0	0.0	1	3.7	0	0.0
Hyperexplexia	0	0.0	1	3.7	0	0.0	1	1.7	0	0.0	1	2.1
Tic disorder	0	0.0	4	14.8	4	25.0	0	0.0	1	3.7	3	6.3
Shuddering attack	2	4.2	0	0.0	0	0.0	2	3.4	2	7.4	0	0.0
Nonspecific PNED	2	4.2	0	0.0	2	12.5	0	0.0	1	3.7	1	2.1
Jitteriness	1	2.1	0	0.0	1	6.3	0	0.0	0	0.0	1	2.1
Benign paroxysmal vertigo	0	0.0	2	7.4	0	0.0	2	3.4	0	0.0	2	4.2
Staring attack	0	0.0	3	11.1	2	12.5	1	1.7	0	0.0	3	6.3
Gastroesophageal reflux	1	2.1	0	0.0	0	0.0	1	1.7	0	0.0	1	2.1
Idiopathic infantile nystagmus	3	6.3	0	0.0	3	18.8	0	0.0	2	7.4	1	2.1

PNED: Paroxysmal non-epileptic disorder

foramen ovale and four patients (16%) had other diagnoses [atrial septal defect (ASD)/ventricular septal defect, ASD, mitral regurgitation, bicuspid aortic regurgitation/ascending aortic dilatation], respectively. On the other hand, pediatric cardiology consultation was performed in 14 patients without breath-holding spells, and secundum ASD, operated transposition of the great artery and aortic dilatation were detected in three patients. None of the patients diagnosed with breath-holding spells underwent consultation except for pediatric cardiology. Among patients with non-breath-holding spells, two patients underwent pediatric gastroenterology consultation, one underwent ear nose throat consultation, and one underwent ophthalmology consultation. The rate of cranial MRI request in patients who had an episode during the examination was statistically higher than those who had no episode during the examination ($p<0.05$), but the difference in terms of request for sleep EEG and video EEG for diagnosis was not statistically significant (Table 4). The definitive diagnosis of epilepsy was present in three patients. One of them was hospitalized in neonatal intensive care unit in the newborn period because of Meconium Aspiration syndrome, and diagnosed as West syndrome. The same patient later developed Sandifer's syndrome after feeding with nasogastric tube, and her complaints regressed after percutaneous endoscopic gastrostomy was performed. The other patient had cryptogenic West syndrome and had a childhood gratification disorder. The last patient underwent surgery at the age of 1 week due to transposition of great arteries and had global development delay and childhood gratification disorder.

The use of iron and piracetam as treatment was significantly higher in patients with breath-holding spells than those with other diagnoses ($p<0.05$) (Table 3). Twenty (69%) of 29 patients

Table 3. Comparison of patients with breath-holding spells and other diagnoses

n		Breath-holding spell		Others		Chi-square	p
		%	n	%			
Gender	Female	12	41.4	24	52.2	0.830	0.362
	Male	17	58.6	22	47.8		
Age group	Infant	17	58.6	31	67.4	0.594	0.441
	Preschool	12	41.4	15	32.6		
Episode during examination	Yes	0	0.0	16	34.8	12.822	**0.000*** **
	No	29	100.0	30	65.2		
Video for diagnosis	Yes	0	0.0	27	58.7	26.596	**0.000*** **
	No	29	100.0	19	41.3		
Sleep EEG request	Yes	3	10.3	17	37.0	6.441	**0.011***
	No	26	89.7	29	63.0		
Cranial MRI request	Yes	1	3.4	10	21.7	4.755	**0.042***
	No	28	96.6	36	78.3		
EEG result	Normal	5	17.2	16	34.8	-	-
	Epilepsy	0	0.0	3	6.5		
	None	24	82.8	27	58.7		
MRI result	Normal	0	0.0	8	17.4	-	-
	Abnormal	0	0.0	2	4.3		
	None	29	100.0	36	78.3		
Iron	Yes	20	69.0	0	0.0	43.260	**0.000*** **
	No	9	31.0	46	100.0		
Piracetam	Yes	5	17.2	0	0.0	8.498	**0.007****
	No	24	82.8	46	100.0		
Final status of the episodes	Yes	9	31.0	23	50.0	-	-
	No	19	65.5	19	41.3		
	Unknown	1	3.4	4	8.7		

EEG: Electroencephalography, MRI: Magnetic resonance imaging
*p<0.05 **p<0.01 ***p<0.001

with breath-holding spells were treated with iron. Only five patients (17%) were given piracetam treatment. Regarding response to treatment, there was no significant difference between those treated with iron and piracetam and those who were not treated. The mean follow-up was 19.17±4.74 months and the median was 20 months. At the end of the follow-up period, episodes disappeared in 39 patients (52%), while 20 (51%) of them had breath-holding spells. The remaining %48 of the patients still had episodes, while the oldest patient with breath-holding spells was 45 months of age, but the frequency of the episodes decreased. Number of episodes had decreased in 21 patients (28%), of which eight patients (38%) had breath-holding spells. There was no change in the frequency of the episodes in nine patients (12%), of which four had gratification disorders, two had idiopathic infantile nystagmus, one had benign myoclonus of early infancy, night terror and shuddering attack. Complaints were increased in one patient (1%) diagnosed with gratification disorder and five patients (7%) could not be reached, so the final status could not be evaluated. At the end of the follow-up period, no new patients with the diagnosis of epilepsy were detected at the final evaluation.

DISCUSSION

There are different diseases according to age in the differential diagnosis of childhood paroxysmal non-epileptic disorders. The most common diagnoses are jitteriness in newborns, breath-holding spells in infants and preschool children, and syncope, migraine and its variants and pseudoseizure in adolescents (5). In our study, breath-holding spells were found to be the most common diagnosis in infants and preschool children, followed by gratification disorder. Jitteriness was not diagnosed in the newborn period in the present study, except in a 2-month-old infant. In cyanotic breath-holding spells, the child screams, cyanoses, jerks, loses and regains consciousness within seconds in the presence of anger and frustration (6). The rates of requesting video, sleep EEG and cranial MRI were significantly lower in our patients with breath-holding spells than in other patients. As in our study, this clinical picture is so stereotypic that recognition of symptoms overcomes diagnostic investigations. In the preschool period, patients with symptoms that may suggest epileptic seizures such as jerking and fainting should be questioned if they cry before the episode. The pallid breath-holding spells resemble syncope, develop after pain and fear, crying is minimal and silent, patients become pale and lose consciousness, and bradycardia occurs (7). All patients in our study were evaluated as cyanotic breath-holding spells. The paleness of the spell with unnoticed triggers may confuse the physicians with the diagnosis of syncope. In our study, pediatric cardiology evaluation was performed in 25 (86%) of 29 patients with breath-holding spells. In a study of 115 patients with long QT syndrome, breath-holding spells were identified as presenting symptom in one (4.3%) of 23 symptomatic patients. In a study conducted in our country, the prevalence of breath-holding spells was found to be 3.6% (8) and it was expressed that the frequency of long QT syndrome was not significantly different from the prevalence in the community. However, evaluation of long QT syndrome was recommended in patients with a history

Table 4. Analysis of the relationship between the presence of episodes during examination and variables

n		Attack during examination		No attack during examination		Chi-square	p
		%	n	%			
Sleep EEG request	Yes	7	43.8	13	22.0	3.035	0.112
	No	9	56.3	46	78.0		
Cranial MRI request	Yes	6	37.5	5	8.5	8.473	0.009*
	No	10	62.5	54	91.5		
EEG result	Normal	7	43.7	14	23.7	-	-
	Epilepsy	1	6.3	2	3.4		
	None	8	50.0	43	72.9		
MRI result	Normal	6	37.5	2	3.4	-	-
	Abnormal	1	6.3	1	1.7		
	None	9	56.3	56	94.9		
Video demand for diagnosis	Yes	7	43.8	20	33.9	0.530	0.467
	No	9	56.3	39	66.1		

EEG: Electroencephalography, MRI: Magnetic resonance imaging
*:p<0.01

of loss of consciousness, persistent episodes over 6 years of age, fainting attacks, arrhythmia and sudden death in the family (9). Iron deficiency anemia has been implicated in the etiology of breath-holding spells, and low hemoglobin (Hb) and inadequate brain oxygenation are risk factors for breath-holding spells (10). According to Cochrane analysis, iron treatment given at a dose of 5 mg/kg/day for 16 weeks has been reported to be effective in reducing the frequency and severity of spells. It has been reported that supplement treatment is much more beneficial especially in children with iron deficiency anemia, and it is correlated with Hb levels, but it may also be useful in children who are not anemic and who do not have lower levels of Hb (11). Piracetam, the cyclic derivative of gamma-aminobutyric acid (GABA), is also used in the treatment of breath-holding spells. It has been suggested that it can prevent breath-holding spells by showing inhibitory effect like GABA does in the brain. In a double blind, placebo-controlled study, there was a significant reduction in spells in the patient group receiving piracetam for 4 months (12). In our study, the rate of iron and piracetam use was significantly higher in patients with breath-holding spells than those with other diagnoses. Twenty patients (69%) with breath-holding spells were treated with iron, while the remaining nine patients (31%) were not treated. Only five patients (17%) were given piracetam treatment. It is known that the spells disappear after the age of 5, regardless of whether treatment is given (7). In our study, there was no patient over 5 years old with a history of breath-holding spells. Home video recordings are the most important tools in the evaluation of childhood paroxysmal non-epileptic disorders after detailed history and observation. Since video EEG examination is not always available, video recordings of episodes may prevent complex examinations and/or the use of unnecessary antiepileptic drugs for the treatment of the disorder in the presence of normal neuromotor development and physical examination findings and normal interictal EEG findings. In our study, video recordings of episodes were requested from all patients diagnosed with gratification disorder and the diagnosis was made by examining the video recordings. Another group of diseases where home video records are valuable is benign myoclonus of infancy. Alvarez suggested the definition of benign polymorphous movement disorder in infancy for the diagnosis of shuddering attacks and benign infantile myoclonus (13). In our study, benign infantile myoclonus was seen in 4 (5.3%) of 75 patients. Due to its paroxysmal character, it is believed that more than half of the patients are mistakenly thought to have West syndrome or one of the epileptic syndromes such as myoclonic infantile epilepsy in the world. However, the diagnosis of epilepsy should be met with suspicion, especially in patients who are less than 18 months old, with typical normal development, normal EEG and episodes with features that separate them from epileptic seizures (13). In our study, epilepsy was not detected in any of these patients during the 2-year follow-up period. The prevalence of paroxysmal non-epileptic disorders was 4.7% in our pediatric neurology outpatient clinic. The prevalence of febrile convulsions and epilepsy constitutes 31% of our pediatric neurology outpatient clinic. In the pediatric epilepsy-monitoring unit where 883 patients were evaluated with long-term video EEG monitorization over a six-year period, 134 patients (15.2%) had paroxysmal non-epileptic disorder. Stereotypic movements, sleep myoclonus, parasomnias and Sandifer syndrome were the most common diagnoses in 26 preschool children. Coincidental epilepsy was reported in 12 patients (46%) in preschool period (14). In our study, epilepsy and coincidental paroxysmal non-epileptic disorders were detected in three patients (4%) simultaneously. The reason for this difference is that the patients referred to the epilepsy monitoring unit due to long term video EEG monitorization request were more likely to have epilepsy and that our study was performed on paroxysmal non-epileptic disorders detected in patients who were admitted to the our outpatient clinic with paroxysmal episodes. However, it should be kept in mind that patients with epilepsy may have simultaneous paroxysmal non-epileptic disorders. For the first time in 1933, Wyllie and Schlesinger described recurrent fever, headache, vomiting and abdominal pain episodes in children as "childhood periodic disorder". Nowadays, childhood periodic syndromes are defined as childhood benign paroxysmal torticollis, childhood benign paroxysmal vertigo, abdominal migraine and cyclic vomiting syndrome (15). In our study, we had two children with benign paroxysmal vertigo. Benign paroxysmal vertigo is characterized by nausea, dizziness and nystagmus attacks that start between 2-4 years of age. It may progress to migraine in the future. Plays such as swings, seesaws that stimulate the labyrinth in the inner ear, fatigue, stressful situations, fever, and awakening from sleep can also trigger attacks (15). Accurate diagnosis will not only prevent unnecessary antiepileptic use, but will also help to eliminate triggering factors. In this study, patients admitted to a pediatric neurology outpatient clinic due to paroxysmal non-epileptic disorders with 16 different diagnoses were evaluated retrospectively. Although the data used in the literature are frequently obtained from video EEG monitoring centers, the data in our study belonged to a pediatric neurology outpatient clinic where patients were referred by a family physician or pediatrician, therefore, the diagnoses were so variable not to be encountered in a video EEG

monitoring center. Albeit our patients did not have video EEG monitoring, no epileptic diagnosis was found in any patient during a follow-up of two years.

CONCLUSION

Paroxysmal non-epileptic disorders are a common diagnostic group in childhood. Patients who cannot be diagnosed accurately and timely are mistakenly diagnosed with epilepsy and they use unnecessary antiepileptic drugs. Since there is no laboratory test to confirm the diagnosis, careful evaluation of clinical findings and home video recordings will provide clues to the diagnosis in many patients.

Ethics

Ethics Committee Approval: Ethics committee approval was received from İstanbul Okmeydanı Training and Research Hospital Ethics Committee (approval number: 09.01.2018/808).

Informed consent: Informed consent was obtained from the parents of all patients who participated in the study.

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REFERENCES

1. Tatli B, Guler S. Non epileptic paroxysmal events in childhood. Türk Pediatr Ars 2017;52:59-65.
2. Mikati MA, Hani AJ. Seizures in childhood. Kliegman RM, F SB, editors. Nelson Textbook of Pediatrics. Philadelphia: Elsevier; 2011.p.2791-959.
3. Uldall P, Alving J, Hansen LK, Kibaek M, Buchholt J. The misdiagnosis of epilepsy in children admitted to a tertiary epilepsy centre with paroxysmal events. Arch Dis Child 2006;91:219-21.
4. Kotagal P, Costa M, Wyllie E, Wolgamuth B. Paroxysmal nonepileptic events in children and adolescents. Pediatrics 2002;110:e46.
5. Paolicchi JM. The spectrum of nonepileptic events in children. Epilepsia 2002;43Suppl3:60-4.
6. Breningstall GN. Breath-holding spells. Pediatr Neurol 1996;14:91-7.
7. Leung AKC, Leung AAM, Wong AHC, Hon KL. Breath-Holding Spells in Pediatrics: A Narrative Review of the Current Evidence. Curr Pediatr Rev 2018;14:22-9.
8. Carman KB, Ekici A, Yimenicioglu S, Arslantas D, Yakut A. Breath holding spells: Point prevalence and associated factors among Turkish children. Pediatr Int 2013;55:328-31.
9. Robinson JA, Bos JM, Etheridge SP, Ackerman MJ. Breath Holding Spells in Children with Long QT Syndrome. Congenit Heart Dis 2015;4:354-61.
10. Hamed SA, Gad EF, Sherif TK. Iron deficiency and cyanotic breath-holding spells: The effectiveness of iron therapy. Pediatr Hematol Oncol 2018;35:186-95.
11. Zehetner AA, Orr N, Buckmaster A, Williams K, Wheeler DM. Iron supplementation for breath-holding attacks in children. Cochrane database Syst Rev 2010;5:CD008132.
12. Sawires H, Botrous O. Double-blind, placebo-controlled trial on the effect of piracetam on breath-holding spells. Eur J Pediatr 2012;171:1063-7.
13. Fernández-Alvarez E. Transient benign paroxysmal movement disorders in infancy. Eur J Paediatr Neurol 2018;22:230-7.
14. Kotagal P, Costa M, Wyllie E, Wolgamuth B. Paroxysmal Nonepileptic Events in Children and Adolescents. Pediatrics 2004;110:e46-e46.
15. Cuvellier J-C, Lépine A. Childhood Periodic Syndromes. Pediatr Neurol 2010;42:1-11.

ORIGINAL ARTICLE

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The Sequencing of the Insulin-like Growth Factor 1 and *Fibulin* 5 Gene Variants in the Pre and Post-menopausal Women with Stress Urinary Incontinence

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Abstract

Objective: Urinary incontinence (UI) is defined as a social problem via involuntary incontinence. Genetic variations that occur especially in muscle and connective tissue can cause the susceptibility stress type UI. We aimed to investigate the variations in insulin-like growth factor 1 and *Fibulin* 5 (*FBLN5*) genes in the pre and post-menopausal women with stress UI (SUI).

Methods: The study consisted of 4 groups: 43 premenopausal women with SUI, 30 premenopausal women without SUI, 43 postmenopausal women with SUI and 30 postmenopausal women without SUI. DNA was isolated from blood samples and sequenced with Illumina®MiSeq. The results were analyzed with SPSS22 (IBM Corp., Armonk, NY, USA) and p value less than 0.05 was considered as statistically significant.

Results: The A>G variant of rs6214 was found 5.26% (2/38) in the patient group and 0% (0/30) in the control group of the premenopausal group ($p>0.05$). This variant was found 2.44% (1/41) in the postmenopausal SUI group ($p>0.05$). The FBLN5 rs929608 variant was not found in any group.

Conclusion: No significant association was found between UI and these variants.

Keywords: Urinary incontinence, rs6214, insulin-like growth factor 1, Fibulin 5

INTRODUCTION

Urinary incontinence (UI) is defined as involuntary incontinence causing social and hygienic problems and is an important symptom of lower urinary tract dysfunction. It can cause depression and anxiety in women and affects women's family and social life significantly in terms of physical and psychological aspects (1). It was determined that some half of the elderly women had UI and some features related to fertility affected the development of UI (2). In a study conducted in Turkey, IU is found in 42.8% of the women andassociated with age, obesity and menopause (3). Stress UI (SUI), the most common type of UI in older women, is defined as involuntary loss of urine during the increase of abdominal pressure in the absence of bladder contractions (4). Various studies showed that genetic variations affect muscle and connective tissue structure leading to UI (5,6). In this respect, examination of the variations in genes that may affect growth in muscle, ligament and cartilage tissue will contribute to revealing the target molecules underlying the pathology of this disease. Insulin like growth factor 1 (IGF1) plays a role in growth (7) and once synthesized, it binds to the receptor in the target cell and triggers proliferation (8). *Fibulin 5* (*FBLN5*) gene encodes an extracellular matrix protein (9) and mutations in this gene were found associated with macular degeneration and hyperelastic skin (10). Thus, we aimed to investigate the effects of variations in the IGF1 and *FBLN5* genes on stress UI in pre and postmenopausal women in our study.

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METHODS

Study Groups and DNA Isolation

The Ethical Committee of the İstanbul Faculty of Medicine, İstanbul University approved our study protocol (no: 2014/921) and informed consent were taken from the patients. Our project was supported by İstanbul University Scientific Research Unit (project no: 2181). In this study, 146 women aged 20-80 years were divided into 4 groups. Group 1: premenopausal women with SUI, Group 2: postmenopausal women with SUI, Group 3: control group as premenopausal women, Group 4: control group as postmenopausal women. Anamnesis of the patients was taken and physical examination was performed. International Urinary Incontinence Consultation Questionnaire-Short Form was filled. Patients with pure stress incontinence were included in the study. Patients with chronic illnesses such as diabetes mellitus, hypertension, patients with mixed incontinence, patients with vaginal prolapse, patients with neurogenic disease, cancer patients, patients taking chemotherapy and radiotherapy treatment were not included in the study. The whole blood samples were taken in ethylenediamine tetraacetic acid tubes and genomic DNA isolated with the use of PureLink DNA extraction kit (Invitrogen, USA) according to the manufacturer's instructions.

Sequencing

'Nextera XT DNA Library Preparation Kit' and 'NexteraXT Index Kit' were used in our study according to Nextera XT amplicon sequencing protocol. After the amount of 1ng DNA per sample was cleared, the samples were diluted with Qubit device and solutions to 0.2 ng/µL. The samples were loaded into the 96-well plate with a volume of 5 µL and the tagmentation step was performed with enzymatic fragmentation and adapter solutions. The tagmented DNA was subjected to polimerase chain reaction (PCR) with index primers and Nextera PCR Mastermix. Each sample were barcoded with separate index adding index sequences to the ends of tagmented DNA with 12 cycles-PCR. After the PCR stage, clean-up was performed with magnetic beads and ethanol. PCR products were quantified and normalized with Qubit. All samples were pooled with buffer solution by equalizing to 2 nmoL. Thus, all sequencing samples were collected in a single tube. The pool DNA library was first subjected to denaturation and dilution steps for loading the samples into the Ilumina MiSeq. Sequencing reaction was carried out by loading to a 600 µL volume cartridge.

Statistical Analysis

SPSS software for Windows, version 22.0 (IBM Corp., Armonk, NY, USA) were used for statistical analysis. Kolmogorov-Smirnov test was used for the normality test. Mann-Whitney U and Fisher exact tests were used to detect the differences in the groups. P value less than 0.05 was considered as statistically significant.

RESULTS

The mean age of 43 premenopausal women with SUI was 45.53±4.1, while the mean age of 30 premenopausal women as control group was 41.3±5.84 and this was not statistically different between the groups ($p>0.05$). On the other hand, the mean age of 43 postmenopausal women with SUI was 61.16±10.45, while the mean age of 30 postmenopausal women as control group was 58.23±4.85 and this was statistically different between the groups ($p<0.05$). There was no significant difference between premenopausal women with SUI (2.5±1.26) and control group (2±1.36) when mean birth numbers were compared ($p>0.05$). Similarly, there was not any significant difference between the mean birth numbers of postmenopausal women with SUI (3.8±2) and control group (3±1.26) ($p>0.05$) (data not shown). Table 1 shows a comparison of IGF1 *rs6214* and *FBLN5 rs929608* variants between groups based on gene sequencing results.There were 86 patients in our SUI groups (43 in pre and 43 in post-menopausal women) and 60 subjects in our control groups. However, we could not reach the results of some of the samples in the sequencing stage and the exact sample numbers were given in Table 1. IGF1 rs6214 was found in premenopausal and postmenopausal women with SUI but these results were not statistically significant to the control groups ($p>0.05$). However, FBLN5 rs929608 variation was not observed in any group.

DISCUSSION

We conducted a case-control study in the pre and post-menopausal women. The variations of IGF1 rs6214 and FBLN5

Table 1. Comparison of the gene sequencing results of groups

Variation	Groups		P value
	Premenopausal women with SUI (n=38)	Premenopausal women as control group (n=30)	
IGF1 rs6214	2 (5.26%)	-	0.308
FBLN5 rs929608	-	-	-
Variation	**Postmenopausal women with SUI (n=41)**	**Postmenopausal women as control group (n=26)**	**P value**
IGF1 rs6214	1 (2.44%)	-	0.612
FBLN5 rs929608	-	-	-

SUI: Stress urinary incontinence, FBLN5: Fibulin 5, IGF1: Insulin like growth factor 1

rs929608 was examined in the SUI. While FBLN5 *rs929608* variation was not found in any group, IGF1 rs6214 variation was found in pre and post-menopausal women.

IGF1, important for protein for cell growth, differentiation and transformation in various tissues (11), plays roles in cell proliferation and apoptosis inhibition after binding to its receptor (12). It has also been reported that IGF1 stimulates fibroblast proliferation, increases collagen synthesis (13), and accelerates the growth and differentiation of striated muscle precursor cells in the human urethral sphincter (14). Furthermore, it was shown that low serum IGF1 levels were found associated with SUI (15). The IGF1 rs6214 variation is a three prime untranslated region (3'-UTR/ G>A) polymorphism. Xu et al. (16) found in a meta-analysis study that rs6214 was associated with a significantly reduced risk of breast cancer under the allele, heterozygote and dominant models and pancreatic cancer under the recessive model. Another meta-analysis study found no association between rs6214 and high myopia (17). Yang et al. (18) found the carriers of rs6214 GG genotype have the risk of low appendicular skeletal muscle mass. IGF1 rs6214 variation wasalso found associated with Barrett esophagus (19) and the development of ischemic stroke (20). Because IGF1 plays a crucial role in hypothalamic-pituitary-ovarian hormone-controlled metabolic processes, Zhao et al. (21) studied rs6214 on age at menarchevariation in Caucasian women and detected the association. However, we did not found the significant association between rs6214 and SUI in pre and post-menopausal women.

FBLN5, a plasma glycoprotein, is encoded by the *FBLN5* gene found in human chromosome 14q31 (22,23) and affects cell proliferation and invasion in various diseases (24,25). Mice with deficiency in the *FBLN5* gene develop systemic heavy elastinopathy including genital prolapse (26). The *FBLN5* gene rs929608 variation (IVS10-45 A>G) is located in intron 10 (27). Khadzhieva et al. (28) showed no association between the FBLN5 rs929608 (T>C) variation and pelvic organ prolapse. Random Forests analysis ranking is found 3 for rs929608 in prostate cancer aggressiveness and Lin et al. (29) suggested that FBLN5 gene variation can influence this disease. However, we did not find this variation in our groups.

Ethics

Ethics Committee Approval: The Ethical Committee of the İstanbul Faculty of Medicine, İstanbul University approved our study protocol (no: 2014/921).

Informed Consent: Written informed consent was obtained from each participicant of this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.H.P., H.A., B.Ç., S.P., E.Ö., Design: H.H.P., H.A., B.Ç., S.P., E.Ö., Data Collection or Processing: E.Ö., Analysis or Interpretation: H.H.P., H.A., B.Ç., S.P., Literature Search: H.H.P., H.A., B.Ç., S.P., E.Ö., Writing: HHP, HA, B.Ç., S.P., E.Ö.

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CONCLUSION

In conclusion, we did not observe any association between SUI, IGF1 rs6214 and FBLN5 rs929608. This result may have been obtained due to the limited number of samples included in our study. However, this study is the first study investigating the relation between IGF1 and *FBLN5* gene variants and SUI.

REFERENCES

1. Kök G, Şenel N, Akyüz A. GATA Jinekoloji Polikliniğine başvuran 20 yaş üstü kadınların ürinerinkontinans açısından farkındalık durumlarının değerlendirilmesi. Gülhane Tıp Dergisi 2006;48:32-6.
2. Bilgili N, Akın B, Ege E, Ayaz S. Prevalence of Urinary Incontinence and Affecting Risk Factors in Women. Turkiye Klinikleri J MedSci. 2008;28:487-93.
3. Öztürk GZ, Toprak D, Basa E. The frequency and the affecting factors of urinary incontinence in women over 35 years old. SETB. 2012;46:170-6.
4. Dursun M, Otunctemur A, Ozbek E, Cakir SS, Polat EC. Impact of the transobturator tape procedure on sexual function in women with stress urinary incontinence. J Obstet Gynaecol Res 2013;39:831-5.
5. Skorupski P, Król J, Starega J, Adamiak A,Jankiewicz K, Rechberger T. An alpha-1 chain of type I collagen Sp1-binding site polymorphism in women suffering from stress urinary incontinence. Am J Obstet Gynecol 2006;194:346-50.
6. Skorupski P, Miotła P, Jankiewicz K, Rechberger T. Polymorphism of the gene encoding alpha-1 chain of collagen type I and a risk of pelvic organ prolapse--a preliminary study. Ginekol Pol 2007;78:852-5.
7. O'Neill BT, Lauritzen HP, Hirshman MF, Smyth G, Goodyear LJ, Kahn CR. Differential Role of Insulin/IGF-1 Receptor Signaling in Muscle Growth and Glucose Homeostasis. Cell Rep 2015;11:1220-35.
8. Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958-2003. J Clin Endocrinol Metab 2004;89:1031-44.
9. Kowal RC, Jolsin JM, Olson EN, Schultz RA. Assignment of fibulin-5 (FBLN5) to human chromosome 14q31 by in situ hybridization and radiation hybrid mapping. Cytogenet Cell Genet 1999;87:2-3.
10. Auer-Grumbach M, Weger M, Fink-Puches R, Papić L, Fröhlich E, Auer-Grumbach P, et al. Fibulin-5 mutations link inherited neuropathies, age-related macular degeneration and hyperelastic skin. Brain 2011;134:1839-52.

11. Delafontaine P, Song YH, Li Y. Expression, regulation, and function of IGF-1, IGF-1R, and IGF-1 binding proteins in blood vessels. Arterioscler Thromb Vasc Biol 2004;24:435-44.

12. LeRoith D. Insulin-like growth factor I receptor signaling--overlapping or redundant pathways? Endocrinology 2000;141:1287-8.

13. Martin P. Woundhealing--aimingforperfect skin regeneration. Science 1997;276:75-81.

14. Sumino Y, Hanada M, Hirata Y, Sato F, Mimata H. The effects of hepatocyte growth factor and insulin-like growth factor-1 on the myogenic differentiation of satellite cells in human urethral rhabdosphincter. Neurourol Urodyn 2010;29:470-5..

15. Ozbek E, Otunctemur A, Sahin S, Ozcan L, Dursun M, Polat E, et al. Low serum Insulin Like Growth Factor - 1 in patients with Stress Urinary Incontinence. Int Braz J Urol 2016;42:787-92.

16. Xu GP, Chen WX, Xie WY, Wu LF. The association between IGF1 Gene 3'-UTR polymorphisms and cancer risk: A Meta-analysis. Medicine (Baltimore) 2018;97:e13829.

17. Zhang D, Zeng G, Hu J, McCormick K, Shi Y, Gong B. Association of IGF1 polymorphism rs6214 with high myopia: A systematic review and meta-analysis. Ophthalmic Genet 2017;38:434-9.

18. Yang CW, Li TC, Li CI, Liu CS, Lin CH, Lin WY, et al. Insulinlike Growth Factor-1 and Its Binding Protein-3 Polymorphisms Predict Circulating IGF-1 Level and Appendicular Skeletal Muscle Mass in Chinese Elderly. J Am Med Dir Assoc 2015;16:365-70.

19. McElholm AR, McKnight AJ, Patterson CC, Johnston BT, Hardie LJ, Murray LJ; Finbar Group.A population-based study of IGF axis polymorphisms and the esophageal inflammation, metaplasia, adenocarcinoma sequence. Gastroenterology 2010;139:204-12.e3.

20. Kim HJ, Kim SK, Park HJ, Chung JH, Chun J, Yun DH, et al. Polymorphisms of IGFI contribute to the development of ischemic stroke. Exp Ther Med 2012;3:93-8.

21. Zhao J, Xiong DH, Guo Y, Yang TL, Recker RR, Deng HW. Polymorphism in the insulin-like growth factor 1 gene is associated with age at menarche in caucasian females. Hum Reprod 2007;22:1789-94.

22. Argraves WS, Tran H, Burgess WH, Dickerson K. Fibulin is an extracellular matrix and plasma glycoprotein with repeated domain structure. J Cell Biol 1990;111:3155-64.

23. Kowal RC, Jolsin JM, Olson EN, Schultz RA. Assignment of fibulin-5 (FBLN5) to human chromosome 14q31 by in situ hybridization and radiation hybrid mapping. Cytogenet Cell Genet 1999;87:2-3.

24. Tu K, Dou C, Zheng X, Li C, Yang W, Yao Y, et al. Fibulin-5 inhibits hepatocellular carcinoma cell migration and invasion by down-regulating matrix metalloproteinase-7 expression. BMC Cancer 2014;14:938.

25. Shi XY, Wang L, Cao CH, Li ZY, Chen J, Li C. Effect of Fibulin-5 on cell proliferation and invasion in human gastric cancer patients. Asian Pac J Trop Med 2014;7:787-91.

26. Budatha M, Roshanravan S, Zheng Q, Weislander C, Chapman SL, Davis EC, et al. Extracellular matrix proteases contribute to progression of pelvic organ prolapse in mice and humans. J Clin Invest 2011;121:2048-59.

27. Elahi E, Kalhor R, Banihosseini SS, Torabi N, Pour-Jafari H, Houshmand M, et al. Homozygous missense mutation in fibulin-5 in an Iranian autosomal recessive cutis laxa pedigree and associated haplotype. J Invest Dermatol 2006;126:1506-9.

28. Khadzhieva MB, Kamoeva SV, Chumachenko AG, Ivanova AV, Volodin IV, Vladimirov IS, et al. Fibulin-5 (FBLN5) gene polymorphism is associated with pelvic organ prolapse. Maturitas 2014;78:287-92.

29. Lin HY, Park H, Park J, Tsai YY. Genetic variations in angiogenesis-related genes in prostate cancer aggressiveness. In: Proceedings of the 102 nd Annual Meeting of the American Association for Cancer Research; 2011 Apr 2-6; Orlando, FL. Philadelphia (PA): AACR; Cancer Res 2011;71(8 Suppl):Abstract nr 2781.

REVIEW

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Approach to Patients with Neurotrauma and Thoracic Trauma and Anesthesia Management with Current Guidelines II

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Abstract

There are many causes of trauma such as traffic and work accidents and falling from height. These patients need systematic management in posttraumatic evaluation, airway management, resuscitation, possible surgical process, intensive care follow-up and treatment. The nature of trauma, uncontrollable bleeding after trauma, coagulation anomalies, hypothermia, shock, acidosis disrupt the normal homeostatic mechanism and are associated with poor clinical course. Another paradox is the nature of unexplained events, insufficient anamnesis information and the necessity of emergency intervention in trauma cases. This section aims to discuss anesthesia management with current guidelines.

Keywords: Neurotrauma, thoracic trauma, anesthesia, guidelines

INTRODUCTION

Anesthesia Management in Trauma

Trauma, which means wound in ancient Greek, is the leading cause of death in the 1-44 age group, and the third cause of death following cancer and cardiovascular disease in all age groups. Trauma is defined as tissue damage characterized by structural changes and physiological disorders due to mechanical, thermal, electrical and chemical energies, ionized or nuclear radiation or absence of essential elements of life such as oxygen and heat. Trauma has many reasons such as traffic accidents, work accidents and falling from height (1,2). These patients need a systematic anesthesia management in posttraumatic evaluation, airway management, resuscitation, possible preoperative and postoperative surgical process, intensive care follow-up and treatment (3). The nature of trauma, uncontrollable bleeding after trauma, coagulation anomalies, hypothermia, shock, acidosis disrupt the normal homeostatic mechanism. Acute coagulopathy caused by high blood loss in major traumas is often associated with poor clinical course in trauma patients (4,5). Another paradox is the nature of unexplained events, insufficient anamnesis information and the necessity of emergency intervention in trauma cases.

Initial Assessment of Trauma

Algorithms have been defined for systemic approach to trauma patients and more than fifty scoring systems have been developed. The Trauma score, which was defined in 1981 by adding respiratory rate and systolic blood pressure to the Triage index, is a widely used scoring system. It was revised in 1989 and Revised Trauma score was formed (Table 1). In order for the trauma centers to systematically engage a modern trauma approach in harmony between the other disciplines, it is necessary to establish national guidelines tailored to the needs and ensure their widespread use. Airway obstruction, severe hemorrhage and hypoxia due to tension pneumothorax may be among the causes of early death due to trauma (6-8). From the moment the trauma patient is met, the first step is to apply the

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ABC stages of cardiopulmonary resuscitation (CPR). Airway must be secured first for effective intervention. All trauma patients should be considered to have cervical damage until they are ruled out, and cervical stabilization should be provided during interventions (Figures 1, 2). In the trauma patient, inadequate anamnesis, full stomach, the possibility of cervical trauma and maxillofacial injury should be considered and the physician should be prepared for difficult airway management. Algorithms have been developed for difficult airway management (Figure 3). Considering the location of the patient's injury and experience of the anesthesiologist, the appropriate method such as oropharyngeal airway, supraglottic airway devices, orotracheal intubation, nasal intubation, tracheotomy or cricothyroidotomy is performed in order to provide airway patency (9). Auscultation and confirmation by capnography should be performed in the patient with secured airway. Circulation should be checked; fluid resuscitation should be started and bleeding, if any, should be controlled. Hypothermia in trauma patients is known to be a cause that increases mortality and morbidity (10). Passive isolation or active heating techniques should be used in these patients, and fluids, blood and blood products to be used in infusion should be heated and unwanted hypothermia should be prevented. Since trauma patients may have life-threatening injuries such as pneumothorax and pericardial tamponade, surgical evaluation should be performed concurrently with CPR. Possible injuries should be determined by laboratory tests, invasive-noninvasive radiological imaging methods and treatment plan should be designed (6,9). In trauma patients, systemic inflammatory response to trauma can be reduced by early and appropriately planned fluid resuscitation (11). Early detection and effective resuscitation of post-traumatic shock-prone patients are life saving. Hypovolemic shock is the inadequate tissue perfusion resulting from decreased intravascular volume. In order to diagnose shock that emerges clinically with findings such as tachypnea, tachycardia, hypotension and low pulse pressure,

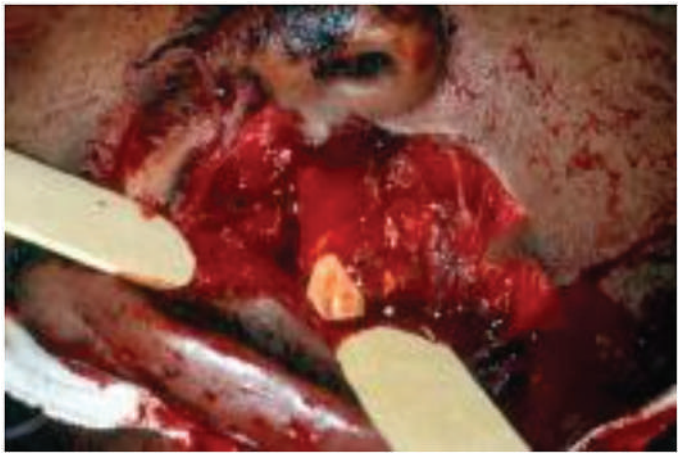

Figure 1. Maxillofacial injury

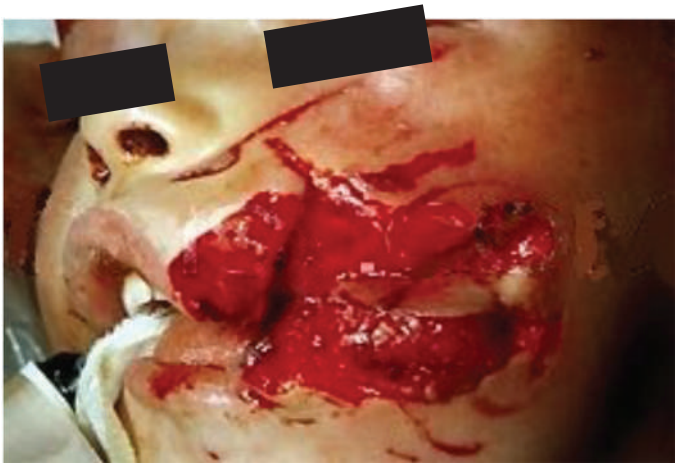

Figure 2. Maxillofacial injury

Table 1. Revised Trauma score

GCS	SBP	RR	Score
13-15	>89	10-29	4
9-12	76-89	>29	3
6-8	50-75	6-9	2
4-5	1-49	1-5	1
3	0	0	0

GCS: Glaskow Coma score, SBP: Systolic blood pressure, RR: Rate ratio

Table 2. Clinical signs of shock according to blood loss

Blood loss	Pulse	SBP	Pulse pressure	Capillary fountain	Respiratory	CNS	Urine output
<15%, 1000 mL	n	↓	n	Delayed	Light tachypnea	Anxiety	20-30 mL/s
30%-40, 1500-2000 mL	>120 weak	↓	↓	Delayed	Serious tachypnea	Confused	20 mL/s
>40%, >2000 mL	>140 nonpalpabl	↓↓	↓↓	Ø	Serious tachypnea	Lethargic	Ø

CNS: Central nervous system, SBP: Systolic blood pressure

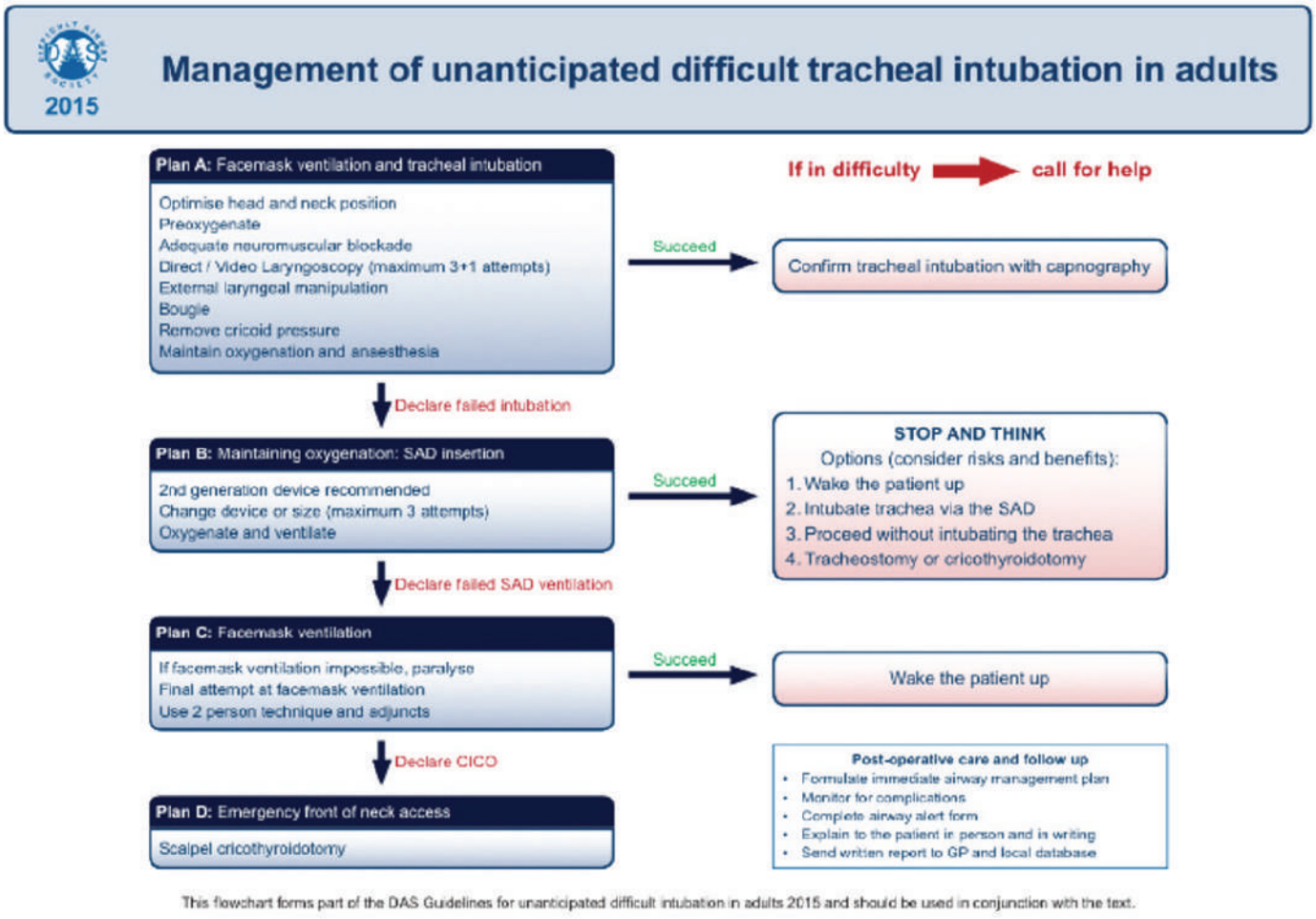

Figure 3. Difficult airline management algorithm
DAS: Difficult Airway Society

lactate measurements, determination of base-excess, and the shock index determined by the ratio of heart rate to systolic blood pressure being above 0.9 may be helpful (Table 2) (12-15). Early fluid replacement is important in correcting hypotension in hypovolemic shock. Crystalloid, colloid fluids, whole blood and blood products are used according to need. More than 10 units of erythrocyte suspension red blood cell (RBC) within 24 hours is called massive blood transfusion (16,17). The answer to question how much transfusion should be performed is still unclear, but massive transfusion protocol with 1:1.5 fresh frozen plasma (FFP)/RBC has been shown to decrease mortality by 74%, leading to an increase in 30-day survival and shorter duration of ventilation and hospitalization (18,19). In massive blood transfusions, citrate-induced hypocalcemia develops especially during the use of FFP, which leads to resistant hypotension. Hypocalcemia below 0.9 mmoL/L should be treated (11,20). The major cause of coagulopathy is the dilution of coagulation factors. Procoagulant factors, fibrinogen, natural anticoagulant factors and antifibrinolytic proteins, which decrease with dilution as a result of massive blood transfusion, lead to coagulopathy. It is important to replace with FFP and platelet suspensions in the early period for treatment. Platelet suspension is recommended if the platelet count is <100.000/mm^3 (21). It has been shown that the use of antifibrinolytic tranexamic acid reduces mortality in patients with bleeding (22). The usefulness of the use of recombinant activated Factor VIIa is controversial, although there are studies showing that early use reduces mortality (23,24). The use of norepinephrine and vasopressin has been found to be beneficial in animal models of trauma, but there are no large-scale studies (11,25). The use of fibrinogen concentrate has been shown to reduce perioperative bleeding by 32% and reduce the need for transfusion (26,27). In the follow-up of these patients, the mean arterial pressure should not be reduced below the brain perfusion pressure and should be higher than 50-60 mmHg. Follow-up of central venous pressure and hourly urine output is beneficial in terms of

showing vital organ perfusion (9). Damage control resuscitation is a relatively new concept in the management of trauma patients consisting of permissive hypotension, prevention of acidemia, reheating and correction of ionized calcium. In patients without contraindications, targeting of mean arterial pressure of "65 mmHg or systolic arterial pressure of" 90 mmHg is called "permissive hypotension" (28). Large amounts of ringer lactate solution to be used in fluid resuscitation may cause cerebral edema. Excessive use of dextrose solutions may cause ischemic brain damage and use of large amounts of isotonic solution may cause hyperchloremic metabolic acidosis. Colloid solutions are effective in providing intravascular volume, but increase the tendency of pulmonary edema with increased hydrostatic pressure. If there is microvascular permeability disorder in the lungs, oncotic pressure increases in the interstitium due to colloid escape from the endothelium, and more fluid may accumulate in the pulmonary interstitium and alveoli, and prolong the need for mechanical ventilation (13). In trauma, insufficient organ perfusion results in metabolic acidosis. Hypothermia, acidosis and coagulopathy are known as the fatal triad of trauma (29). Acid-base imbalance can be eliminated by hydration and correcting organ perfusion. Uncorrected lactic acidosis is defined as an independent risk factor for multiorgan failure (30). Multiorgan failure may occur 12 hours after shock after trauma and may be delayed up to 7-10 days, which is one of the most important causes of mortality (13,31).

ANESTHESIA IN TRAUMA

Sedation Anesthesia

In order to perform simple fracture reduction, shoulder dislocation, tube thoracostomy, and cardioversion, patients may need anesthesia applications that protect cardiorespiratory functions and protective reflexes (32). As in all anesthesia applications, patient needs to be evaluated for sedoanalgesia, monitorized and the necessary emergency response equipment should be available. Regarding anesthetic agent, single or combined applications of conventional benzodiazepine (midazolam), propofol, ketamine, ketofol and fentanyl have been studied. In these studies, ketofol has been found to be superior due to rapid onset, effective sedation depth, low values in sensation of pain, and high patient and staff satisfaction (33-35).

General Anesthesia

General anesthesia begins with rapid induction and rapid intubation strategy, but there is no optimal anesthetic agent for patients with hemorrhagic shock. The most commonly used agents for induction are thiopental sodium, propofol, etomidate and ketamine. Thiopental sodium is a barbiturate commonly used in induction since 1934. Since intracranial pressure (ICP) increases due to cerebral hemorrhage and edema in head trauma, barbiturates, which lead to a decrease in cerebral blood flow (CBF) and ICP by cerebral vasoconstriction, may be preferred (6,36). However, it has been reported that induction with thiopental sodium increases critical respiratory problems approximately 2-fold in the postoperative period. The dose of intravenous (IV) induction is 3-6 mg/kg (6,37). As it causes venous dilatation and hypotension, it is recommended to reduce the dose in patients with unstable hemodynamics (38). Having high lipophilic properties cause propofol to pass through the blood-brain barrier and reach the central nervous system, causing the effect to start very quickly and to be short-term. The dose of IV induction is 1-2.5 mg/kg. It reduces CBF and ICP, and may be preferred in patients with head trauma, but it has myocardial depressant effect. Caution should be exercised in the use of propofol, which causes peripheral vasodilation and reduces systemic vascular resistance, in hemodynamically unstable trauma patients (6,39). Etomidate is an induction agent that acts rapidly with gamma-aminobutyric acid receptor stimulation. The dose of IV induction is 0.3 mg/kg (6). It is widely used in trauma patients because it has a rapid onset and does not impair hemodynamics (40). In traumatic brain injury, etomidate may be preferred because it provides cerebral protection by decreasing cerebral metabolic rate of oxygen (CMRO2), CBF and ICP (41). It has been shown that etomidate can lead to adrenal suppression even with a single dose in rapid intubation (42). Etomidate use in trauma patients was also associated with nosocomial pneumonia (43). Ketamine increases arterial blood pressure, heart rate and cardiac output through central stimulation of the sympathetic nervous system and inhibition of norepinephrine reuptake. It shows its effect on N-methyl-D-aspartate receptors and is a dissociative agent (41). It is suitable for use in cardiac tamponade and hypovolemic patients in trauma, but may lead to cardiac hypotension and cardiovascular collapse in hemorrhagic shock patients with previous maximum sympathetic stimulation and previously depleted catecholamines, it should be administered in small doses by titrating in trauma patients (6,44). It is a potent bronchodilator and a good option for induction, especially in asthma patients with reactive airway. It increases CMRO2, CBF and ICP in accordance with cardiac effects (6,41,45). This limits the use of ketamine in traumatic brain injuries. However, some studies have reported that it increases cerebral perfusion and has no significant effect on ICP (46). Compared with opioids, the use of ketamine in trauma patients has been associated with an

increase in acute and posttraumatic stress disorder, but there are also studies showing the antidepressant effect (47-49). For rapid intubation, succinylcholine, rocuronium and vecuronium may be used as muscle relaxants. Succinylcholine is a depolarizing agent with rapid onset of action (30s) and its duration of action is quite short (5-10 minimum). It can be administered at doses of 1-2 mg/kg IV or 3-4 mg/kg intramuscular. It may be preferred in trauma patients requiring urgent and serial intubation (45). However, it may cause hyperpotasemia in patients with burns and multiple traumas. Succinylcholine is known to increase ICP and intraocular pressure, which can be reduced by the use of lidocaine (1.5 mg/kg) before administration. It should not be used in eye and head trauma (6,50). Rocuronium is a nondepolarizing agent and IV dose is 0.5-0.8 mg/kg for intubation. In cases where rapid intubation is required, administration at a dose of 1 mg/kg creates an effect equivalent to succinylcholine. Another way for rapid intubation is to apply the priming technique. In this technique, 0.06 mg/kg rocuronium is administered IV before the induction and intubation can be performed within 60 seconds with an IV dose of 0.6 mg/kg (45,51). Intubation success rates of succinylcholine and rocuronium were found to be similar in the studies performed in the emergency departments (52). It has been shown that the rocuronium effect can be rapidly eliminated by using 16 mg/kg sugammadex and returned to spontaneous respiration, especially when an unexpected difficult airway is encountered (53).

The intubation dose of vecuronium is 0.08-0.12 mg/kg and its use is limited because it has a long-onset duration of action (80-140s) and in some patients exacerbates bradycardia caused by opioids (6,44). There are many studies focused on ischemic reperfusion injury and organ damage due to the cardioprotective effects of inhalation anesthetics (54). In trauma patients, minimum alveolar concentration (MAC) values of inhalation anesthetics should be reduced (≤0.5 MAC) (6). Patients with severe hypovolemia may not tolerate the vasodilator effect of inhalation anesthetics. In order to avoid increased cerebral blood flow and ICP in traumatic brain injury, the dose of volatile agents should be titrated to less than 1 MAC. Inhalation anesthetics with low blood-gas partition coefficients such as sevoflurane or desflurane may be preferred. Nitrous oxide is not used in trauma patients because it increases cerebral oxygen consumption, ICP, increases pulmonary vascular resistance and causes diffusion hypoxia (9,55). Since opioids show analgesic activity by binding to specific receptors in the central nervous system and other tissues, their combination with other anesthetic drugs may result in marked myocardial depression. It can prevent tissue damage by improving microcirculation in hemorrhagic shock. Fentanyl is a preferred opioid in trauma patients because of its minimal effects on hemodynamics. Fentanyl suppresses increased catecholamines, antidiuretic hormone and cortisol secretion in stress response. It prevents bronchoconstriction against airway stimulation during intubation. However, it may cause chest wall rigidity (6,56). In many studies, it was emphasized that opioid use should be titrated according to the response (50). Midazolam, a fast acting benzodiazepine, provides sedation and amnesia. Induction dose is 0.2 mg/kg IV. It has no analgesic effect and its use is limited in trauma patients because it decreases mean arterial blood pressure. It is frequently used in low dose (0.05 mg/kg) in the emergency department (37,57).

Regional Anesthesia

In trauma, regional anesthesia is contraindicated if the patient is not hemodynamically stable. However, regional technique may be used to increase peripheral blood flow by vasodilatation by blocking sympathetic innervation especially in amputations and extremity trauma with stable hemodynamics (6). Brachial plexus blocks are more common in upper extremity injuries and central blocks are more common in lower extremity injuries. Cases where central and peripheral blocks are applied together have also been reported (58,59). Trauma is a chaotic process involving many pathophysiological changes. In order for anesthetists to cope with high mortality and morbidity in trauma, trauma management procedures should be a good implementer of algorithms. Rapid resuscitation in the traumatic patient, effective surgical hemostasis, and effective struggle with hypothermia, acidosis and coagulopathy will be the secret of success.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: N.T., T.M., A.A., M.E., Design: N.T., T.M., A.A., M.E., Data Collection or Processing: T.M., A.A., C.K.B., M.E., Analysis or Interpretation: N.T., T.M., A.A., M.E., Literature Search: T.M., S.T., A.A., M.E., Writing: T.M., C.K.B., S.T., A.A., M.E., İ.A.

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REFERENCES

1. Khorram-Manesh A. Europe on Fire; Medical Management of Terror Attacks - New Era and New considerations. Bull Emerg Trauma 2016;4:183-5.

2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-128.

3. American Society of Anesthesiologists. Statement of principles: trauma anesthesiology. In: Standards, Guidelines, Retrieved on 16 October 2013 from http://www.asahq.org/For-Members/Standards-Guide lines-and-Statements.

4. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, et al. Management of bleeding following major trauma: an updated European guideline. Crit Care 2010;14:R52.

5. Ganter MT, Pittet JF. New insights into acute coagulopathy in trauma patients. Best Pract Res Clin Anaesthesiol 2010;24:15-25.

6. Morgan EG, Mikhail MS, Murray MJ, Larson CP. Tulunay M, Cuhruk H, editörler. Klinik Anesteziyoloji. Ankara: Güneş Kitabevi Ltd. Şti; 2004.

7. Anderson NK, Jones AD, Martin EE, Thies RF, Baxter D, Marienau ME, et al. Anesthetic care of the trauma patient: development of a Web-based resource. AANA J 2007;75:49-56.

8. Hajjar WM, Alsubaie N, Nouh TA, Al-Nassar SA. Is it safe to use frova airway intubating device during tracheal intubation in difficult airway patient with multiple and chest trauma. Saudi J Anaesth 2016;10:477-9.

9. Stane JK, grande CM. Anesthesia for trauma. In: Miller RD, editor. Anesthesia. Fift ed. Phidelphia: Churchill Livingstone; 2000.p.2157-72.

10. Tsuei BJ, Kearney PA. Hypothermia in the trauma patient. Injury 2004;35:7-15.

11. Tobin JM, Varon AJ. Update in trauma anesthesiology: perioperative resuscitation management. Anesth Analg 2012;115:1326-33.

12. Şahin A, Ertekin C, Güloğlu R, Yamaner S, Bilsel Y. Şok parametrelerinin şok ve mortaliteyi belirlemedeki etkinlikleri. Ulusal Travma Derg 1997;3:233-42

13. Tümay V, Tokyay R. Hipovolemik Şok. Yoğun Bakım Derg 2002;2:246-54

14. Rady MY, Smithline HA, Blake H, Nowak R, Rivers E.A comparison of the shock index and conventional vital signs to identify acute, critical illness in the emergency department. Ann Emerg Med 1994;24:685-90.

15. Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: mechanism, identification and effect. Curr Opin Crit Care 2007;13:680-5.

16. Brummel-Ziedins K, Whelihan MF, Ziedins EG, Mann KG. The resuscitative fluid you choose may potentiate bleeding. J Trauma 2006;61:1350-8.

17. Ho AM, Karmakar MK, Dion PW.Are we giving enough coagulation factors during major trauma resuscitation? Am J Surg 2005;190:479-84.

18. Dente CJ, Shaz BH, Nicholas JM, Harris RS, Wyrzykowski AD, Patel S, et al. Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. J Trauma 2009;66:1616-24.

19. Cotton BA, Au BK, Nunez TC, Gunter OL, Robertson AM, Young PP. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. J Trauma 2009;66:41-8.

20. Lier H, Krep H, Schroeder S, Stuber F. Preconditions of hemostasis in trauma: a review. The influence of acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. J Trauma 2008;65:951-60.

21. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, et al. Management of bleeding following major trauma: an updated European guideline. Crit Care 2010;14:52.

22. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): arandomised, placebo-controlled trial. Lancet 2010;376:23-32

23. Spinella PC, Perkins JG, McLaughlin DF, Niles SE, Grathwohl KW, Beekley AC, et al. The effect of recombinant activated factor VII on mortality in combat-related casualties with severe trauma and massive transfusion. J Trauma 2008;64:286-93.

24. Spinella PC, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. Blood Rev 2009;23:231-40.

25. Sheffy N, Chemsian RV, Grabinsky A. Anaesthesia considerations in penetrating trauma. Br J Anaesth 2014;113:276-85.

26. Karlsson M, Ternström L, Hyllner M, Baghaei F, Flinck A, Skrtic S, et al. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. Thromb Haemost 2009;102:137-44.

27. Rahe-Meyer N, Pichlmaier M, Haverich A, Solomon C, Winterhalter M, Piepenbrock S, et al. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. Br J Anaesth 2009;102:785-92

28. Lier H, Böttiger BW, Hinkelbein J, Krep H, Bernhard M. Coagulation management in multiple trauma: a systematic review. Intensive Care Med 2011;37:572-82.

29. Ryan Gerecht. CMTE Trauma's Lethal Triad of Hypothermia, Acidosis & Coagulopathy Create a Deadly Cycle for Trauma Patients Journal of emergency medical service Wed, Aprl 2, 2014

30. Mahonee L, Flaherty M. Travma için anestezi. In: Duke J, editor. Dikmen Y, çeviri editörü. Anestezinin Sırları. 2. Baskı. İstanbul: Nobel Tıp Kitabevleri; 2006.p.287-91.

31. Dewar D, Moore FA, Moore EE, Balogh Z. Postinjury multiple organ failure. Injury 2009;40:912-8.

32. Godwin SA, Burton JH, Gerardo CJ, Hatten BW, Mace SE, Silvers SM, et al. Clinical Policy: Procedural Sedation and Analgesia in the Emergency Department. Ann Emerg Med 2017;70:758.

33. Andolfatto G, Abu-Laban RB, Zed PJ, Staniforth SM, Stackhouse S, Moadebi S, et al. Ketamine-propofol combination (ketofol) versus propofol alone for emergency department procedural sedation and analgesia: a randomized double-blind trial. Ann Emerg Med 2012;59:504-12.e1-2.

34. Nejati A, Moharari RS, Ashraf H, Labaf A, Golshani K. Ketamine/propofol versus midazolam/fentanyl for procedural sedation and analgesia in the emergency department: a randomized, prospective, double-blind trial. Acad Emerg Med 2011;18:800-6.

35. Andolfatto G, Willman E. A prospective case series of pediatric procedural sedation and analgesia in the emergency department using single-syringe ketamine-propofol combination (ketofol). Acad Emerg Med 2010;17:194-201.

36. Yaghoobi S, Khezri MB, Alamouti AM. A Pilot Study of Cerebral and Hemodynamic Changes During Sedation with Low Dose of Thiopental Sodium or Propofol in Patients with Acute Brain Injury. J Clin Diagn Res 2015;9:UC05-7.

37. Caro D, Sedation or induction agents for rapid seqence intubation in adults. Ed. Walls RM. www.uptodate.com 2015 UpToDate.

38. Reich DL, Hossain S, Krol M, Baez B, Patel P, Bernstein A, et al. Predictors of hypotension after induction of general anesthesia. Anesth Analg 2005;101:622-8

39. Fields AM, Rosbolt MB, Cohn SM. Induction agents for intubation of the trauma patient. J Trauma 2009;67:867-9.

40. Hinkewich C, Green R. The impact of etomidate on mortality in trauma patients. Can J Anaesth 2014;61:650-5.

41. Agarwala A, Dershwitz M. Intravenous induction agents. In: Vacanti CA, Sikka PK, Urman RD, Dershwitz M, Segal BS, editors. Essential clinical anesthesia. New York: Cambridge University Press; 2011.p.227-32.

42. Chan CM, Mitchell AL, Shorr AF. Etomidate is associated with mortality and adrenal insufficiency in sepsis: a meta-analysis. Crit Care Med 2012;40:2945-53.

43. Asehnoune K, Mahe PJ, Seguin P, Jaber S, Jung B, Guitton C, et al. Etomidate increases susceptibility to pneumonia in trauma patients. Intensive Care Med 2012;38:1673-82.

44. Stollings JL, Diedrich DA, Oyen LJ, Brown DR. Rapidsequence intubation: a review of the process and considerations when choosing medications. Ann Pharmacother 2014;48:62-76.

45. Bassett MD, Smith CE. General anesthesia for trauma. In: Varon AJ, Smith CE, editors. Essentials of trauma anesthesia. New York: Cambridge University Press; 2012.p.76-94.

46. Filanovsky Y, Miller P, Kao J. Myth: ketamine should not be used as an induction agent for intubation in patients with head injury. CJEM 2010;12:154-7.

47. Schönenberg M, Reichwald U, Domes G, Badke A, Hautzinger M. Ketamine aggravates symptoms of acute stress disorder in a naturalistic sample of accident victims. J Psychopharmacol 2008;22:493-7.

48. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47:351-4.

49. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006;63:856-64.

50. Robert A. Sikorski A. Ken Koerner L. Yvette Fouche-Weber Samuel M. Galvagno Jr. Choice of General Anesthetics for Trauma Patients. Curr Anesthesiol Rep 2014;4:225-32.

51. Suzuki T, Aono M, Fukano N, Kobayashi M, Saeki S, Ogawa S. Effectiveness of the timing principle with high-dose rocuronium during rapid sequence induction with lidocaine, remifentanil and propofol. J Anesth 2010;24:177-81.

52. Patanwala AE, Stahle SA, Sakles JC, Erstad BL. Comparison of succinylcholine and rocuronium for first-attempt intubation success in the emergency department. Acad Emerg Med 2011;18:10-4.

53. Lee C, Jahr JS, Candiotti KA, Warriner B, Zornow MH, Naguib M. Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium: a comparison with spontaneous recovery from succinylcholine. Anesthesiology 2009;110:1020-5.

54. De Hert SG, Turani F, Mathur S, Stowe DF.Cardioprotection with volatile anesthetics: mechanisms and clinical implications. Anesth Analg 2005;100:1584-93.

55. Enlund M, Edmark L, Revenäs B. Is nitrous oxide a real gentlemen? Acta Anaesthesiol Scand 2001;45:922-3.

56. Brookes ZL, Brown NJ, Reilly CS. The dose-dependent effects of fentanyl on rat skeletal muscle microcirculation in vivo. Anesth Analg 2003;96:456-62

57. Sagarin MJ, Barton ED, Sakles JC, Vissers RJ, Chiang V, Walls RM, et al. Underdosing of midazolam in emergency endotracheal intubation. Acad Emerg Med 2003;10:329-38.

58. Çelik F, Tüfek A, Temel V, Kavak GO. Combination of spinal anesthesia and peripheral nerve block: Case report. Dicle Med J 2010;37:401-3.

59. Kıroğlu Ş, Aldemir MT, Süren M, Çömlekçi M, Peker AG, Ertuğrul F. Üç olguda üst ekstremite periferik sinir bloğu ile birlikte spinal anestezi uygulaması. Bildiri Özeti P-RA-94 TARK 2008.