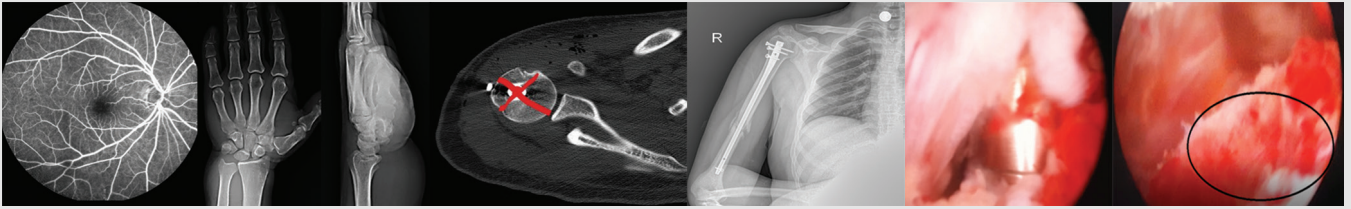


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Books with a Single Author: Sweetman SC. *Martindale the Complete Drug Reference*. 34th ed. London: Pharmaceutical Press;2005.

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

Conference Proceedings: Bengissson 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 İlişkiler. 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 Dent 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/ncidod/EID/cid.htm](http://www.cdc.gov/ncidod/EID/cid.htm).

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Retrospective Analysis of Tumor Location with Residue Rates in High-grade Glial Tumors

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Bezmialem Vakıf University Faculty of Medicine, Department of Neurosurgery, İstanbul, Turkey

Abstract

Objective: Glioblastoma is the most commonly seen and quite an aggressive type of primary brain tumor. Location of the tumor, age, and sex are important prognostic factors. The aim of this study was to present the retrospective data about glioblastoma patients in which location of glioblastoma and calculation of residual tumor tissue was performed at our clinic.

Methods: Tumor location, age and sex distributions, and residue presence in control magnetic resonance imaging (MRI) of 99 patients treated at our clinic within the last two years with a high-grade glial tumor were examined retrospectively. Variables included in the analysis were demographic data and the presence of residue on the control MRI within 24 hours. Chi-square test was used for comparisons. The data were analyzed by SPSS version 24.0 package program.

Results: Of a total of 99 glioblastomas, the male/female ratio was 2:1, the average age of the patients was 54 ± 37 (minimum: 18, maximum: 88; standard deviation: 15.08). In MRI, tumor was located at the frontal and temporal lobes with maximal percentile. In 55 of the cases, total resection was seen. In 38 of the cases, residue under 10% was seen, and in 6 of the cases, residual mass over 10% was seen. Relationship of tumor location with residual mass was not statistically significant ($p=0.562$).

Conclusion: The aim of neurosurgery in glioblastomas is surgical excision to remove as much tumor as possible with minimal neurological deficit. Preoperative characterization of the tumor through current imaging methods makes a significant contribution to mortality and morbidity. New prognostic parameters are needed based on new surgical approaches and imaging techniques.

Keywords: Glioblastoma, glioma, magnetic resonance imaging, prognosis, residual mass

INTRODUCTION

High-grade gliomas are the most common brain tumors that form about 80% of the primary malignant tumors of the brain (1,2). In addition to the basic cell type and differentiation, their immunological profiles constitute the World Health Organization (WHO) 2016 classification system. Among them, the most aggressive and most common glioma is grade 4 glioblastoma. It is more common in men than in women, but its etiology is unknown. Neurosurgical resection, radiotherapy, and chemotherapy are the current standard treatments. Despite all advanced treatment combinations, the average survival is

less than 15 months. Patient's age at the preoperative period and tumor location are some of the current factors that determine the prognosis. In adult age groups, the incidence of high-grade glial tumors increases (3-5). Advanced age, especially over 70, is seen as a sign of poor prognosis. There are brain areas functionally defined as elegant regions which cause serious neurological loss when damaged. The factor limiting the surgical approach to these areas is the potential magnitude of neurological loss. Safe total resection is the surgical goal in glial tumors, and the amount of resection is one of the most important factors determining prognosis (6-8). The aim



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of our study was to examine the effect of tumor location on postsurgical residue rate in 99 patients.

METHODS

Approval for this retrospective study was obtained from the Ethics Committee for Noninterventional Studies of our University Hospital, Bezmialem Vakıf University Faculty of Medicine (14/159). The study was planned so as not to pose any risk to the patients receiving treatment. Data of 99 patients who applied to our clinic between January 2016 and January 2018 and diagnosed with grade 4 glioblastoma were retrospectively analyzed. Patients who had needle biopsy or excisional biopsy via navigation were not included in the list. Patients who had WHO grade 1, 2, or 3 gliomas were also excluded (Table 1). Tumor volume at the time of admission and post-surgical residue volumes were calculated using Leksell Gamma Plan version 10.1 (Treatment planning software for Leksell Gamma Knife® Perfexion™, Stockholm) (Figure 1A, 1B).

Statistical Analysis

The analysis was performed by the chi-square test ($p < 0.005$) using SPSS (Statistical Package for the Social Sciences) version 24.0 (SPSS Inc, Chicago, IL, USA).

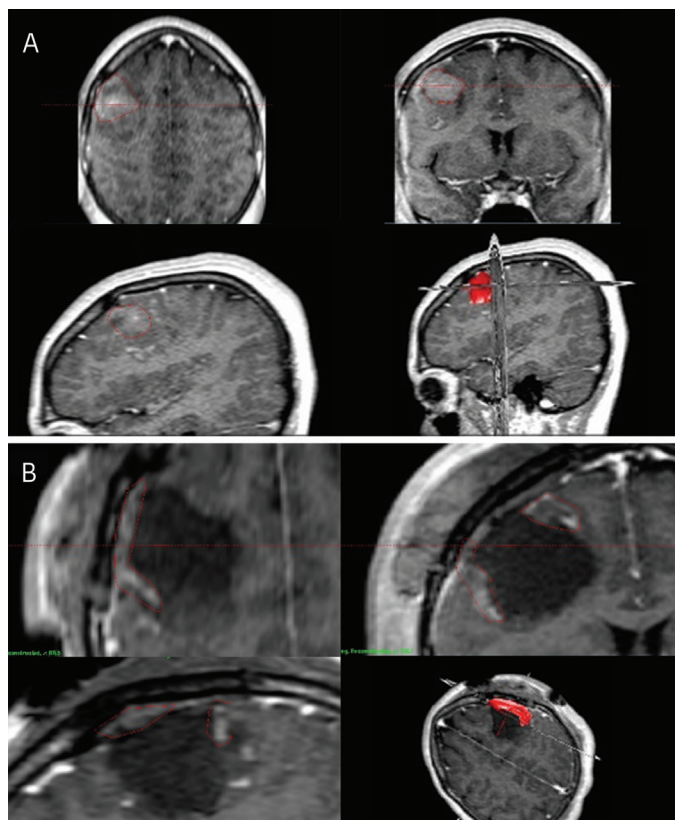


Figure 1. Tumor (A) and residual mass (B) volumes with Leksell Gamma Plan version 10.1 (Treatment planning software for Leksell Gamma Knife® Perfexion™)

RESULTS

There were 60 males (60.6%), 39 females (39.4%) and their mean age was 54.37 (minimum: 18, maximum: 88; standard deviation: ± 15.08) (Table 1). In magnetic resonance imaging (MRI), tumor was located in right frontal lobe in 16 patients (16.2%), left temporal lobe in 10 patients (10.1%), left occipitotemporal lobe in 2 patients (2%), right parietooccipital lobe in 4 patients (4.0%), left parietal lobe in 6 patients (6.1%), bilateral frontal lobes in 2 patients (2%), right parietal lobe in 8 patients (8.1%), right occipitotemporal lobe in a patient (1%), right temporal lobe in 12 patients (12.1%), right occipital lobe in 5 patients (5.1%), right frontotemporoparietal lobe in 2 patients (2%), left frontal lobe in 15 patients (15.2%), left frontotemporal lobe in 4 patients (4%), left occipital lobe in 6 patients (6.1%), and left temporoparietal lobe in 4 patients (4%) (Table 2, Graphic 1). Total resection was

Table 1. Age and sex distribution of glioblastoma patients

		Sex		Total
		Male	Female	
Age	18-30	5	2	7
	31-50	16	14	30
	51-60	17	6	23
	61-88	22	17	39
Total		60	39	99

Table 2. Tumor locations in pretreatment MRI with contrast

Location	Number	%
Right frontal	16	16.2
Left temporal	10	10.1
Left occipitotemporal	2	2.0
Right parietooccipital	4	4.0
Left parietal	6	6.1
Suprasellar	1	1.0
Left temporooccipital	1	1.0
Bifrontal	2	2.0
Right parietal	8	8.1
Right occipitotemporal	1	1.0
Right temporal	12	12.1
Right occipital	5	5.1
Right frontotemporoparietal	2	2.0
Left frontal	15	15.2
Right frontotemporal	2	2.0
Left Occipital	6	6.1
Left frontotemporal	2	2.0
Left temporoparietal	4	4.0
Total	99	100.0

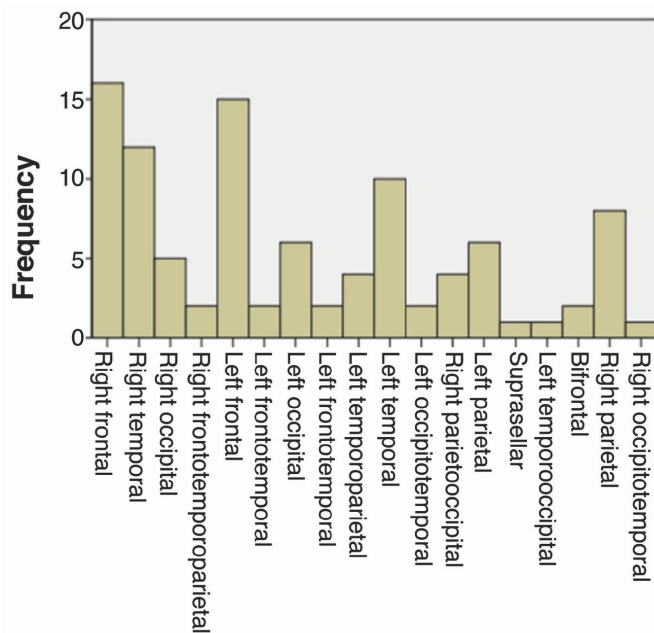
MRI: Magnetic resonance imaging

found in 55 patients (55.6%), lower than 10% residue in 38 patients (38.4%), and higher than 10% residue in 6 patients (6.1%) (Graphic 2, Graphic 3).

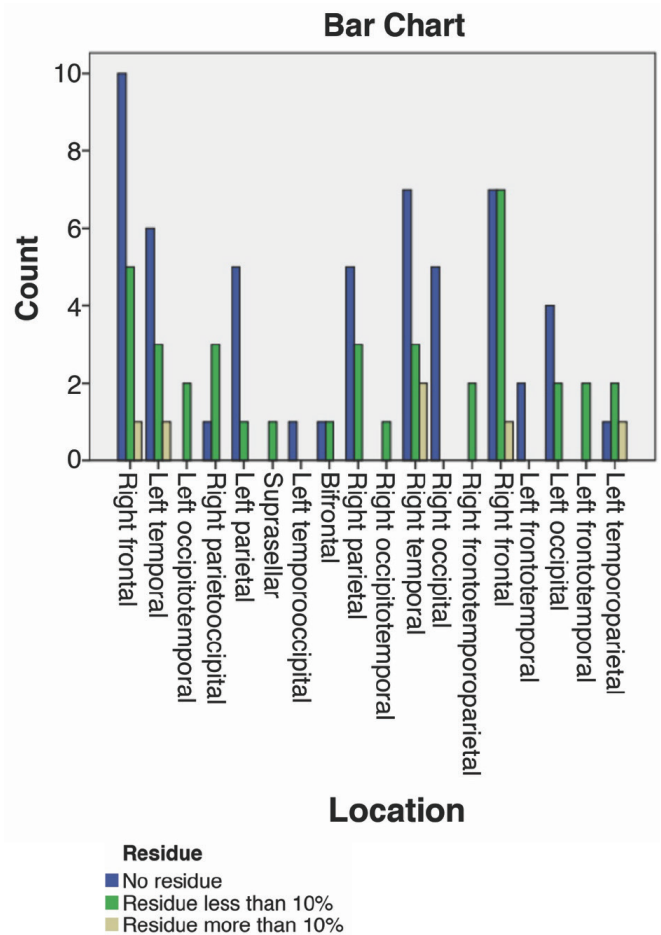
DISCUSSION

The mean age of onset of glioblastoma in the literature was 54-60 and in our study it was 55. The frequency in male sex was in parallel with the literature. The frontal lobe, which was the most common location in literature, was also the most common location in our study (Table 3). No statistically significant relation was found between tumor location and the rates of postsurgical residue (p=0.562) (Table 4). This finding was not consistent with the literature.

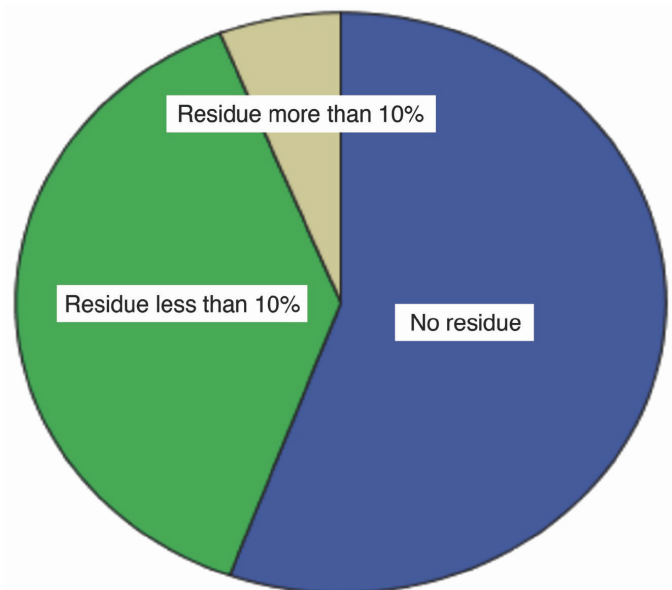
Glioblastoma is characterized by malignant cell proliferation at different steps, neovascularization in aberrant structure and function, various degrees of infiltration, and treatment resistance. Today, glial tumor, glioma, and brain tumor can be used interchangeably (9). Many prognostic factors have been defined to predict the survival of the patients with glioblastoma. These include the age of the patient at the time of diagnosis, preoperative performance score (especially the Karnofsky Performance score), tumor location, characteristic features of tumor in preoperative MRI, history of reoperation for recurrent tumor, radiotherapy, and chemotherapy. These factors are related to one another. Despite technological advances, age, location, and amount of surgery have remained



Graphic 1. Frequency of tumor locations in pretreatment MRI with contrast
MRI: Magnetic resonance imaging



Graphic 2. The association between residue rates and tumor locations



Graphic 3. Residue rates in MRI with contrast performed at postoperative first 24 hours. We found that 55.6% of the cases had a total resection, 38.4% had residue below 10%, and 6.1% had residue above 10%
MRI: Magnetic resonance imaging

Table 3. Distribution of tumor-residue rates according to locations in contrasted and perfusion MRI evaluations

		Residue			Total
		No residue	Residue below 10%	Residue above 10%	
Location	Right frontal	10	5	1	16
	Left temporal	6	3	1	10
	Left occipitotemporal	0	2	0	2
	Right Parietooccipital	1	3	0	4
	Left parietal	5	1	0	6
	Suprasellar	0	1	0	1
	Left temporooccipital	1	0	0	1
	Bifrontal	1	1	0	2
	Right parietal	5	3	0	8
	Right occipitotemporal	0	1	0	1
	Right temporal	7	3	2	12
	Right occipital	5	0	0	5
	Right frontotemporoparietal	0	2	0	2
	Left frontal	7	7	1	15
	Left frontotemporal	2	0	0	2
	Left occipital	4	2	0	6
	Left frontotemporal	0	2	0	2
Left temporoparietal	1	2	1	4	
Total		55	38	6	99

MRI: Magnetic resonance imaging

Table 4. Results of the chi-square test

	Value	df	Asymp. Sig. (2-sided)
Pearson chi-square	32.085 ^a	34	0.562
Likelihood ratio	37.528	34	0.311
Linear-by-Linear association	0.009	1	0.926
N of valid cases	99		

^a48 cells (88.9%) have expected count less than 5, the minimum expected count is 0.06

as major prognostic factors in the literature for many years (10,11).

Age is an important prognostic factor in glioblastomas (12). In our study, the mean age of admission was 55 years. In the literature, the peak age of incidence is 54-60 (6,13). Our finding is consistent with the literature. Eighteen months survival rate after the diagnosis was 60% below 40 years of age and 8% above 60 years of age. In another study, two-year survival was only 2% in the group at or above 65 years of age and 30% in the group at or below 45 years of age. In all glial tumors, the frequency in males is higher than the frequency in females. Males were also predominant in our study. However, the prognostic effect of

sex has not been proven. It can't be used as a prognostic factor (12,14,15).

The location of the lesion is the most important prognostic factor in neuroimaging (16). For this purpose, MRI is the first method to be used in clinical practice. It guides surgical treatment by revealing the shape, volume, and characteristics of the lesion. Perfusion weighted MR imaging plays major roles in both the detailed demonstration of tumoral tissue and the determination of surgical resection margins by dynamic contrast-enhanced MR and dynamic susceptibility contrast MR (16,17) (Figure 2).

In three different studies in which three-dimensional volumetric analysis was performed with MRI, gross-total tumor resection (>98% tumor tissue removal) increased the average life span by 2-8 months compared to subtotal resection (50-98% tumor tissue removal) (18). On the other hand, there are few studies showing that there is not always a correlation between resection rate and average survival time. Therefore the need for extensive and homogenized studies was emphasized (19). Prognosis is very poor in deep brain areas like thalamic region or brainstem gliomas. Compression to nuclei in their neighborhood and difficulty to access surgically are among the causes of poor prognosis. Cranial nuclei and sensitive structures such as corticospinal and cortico-

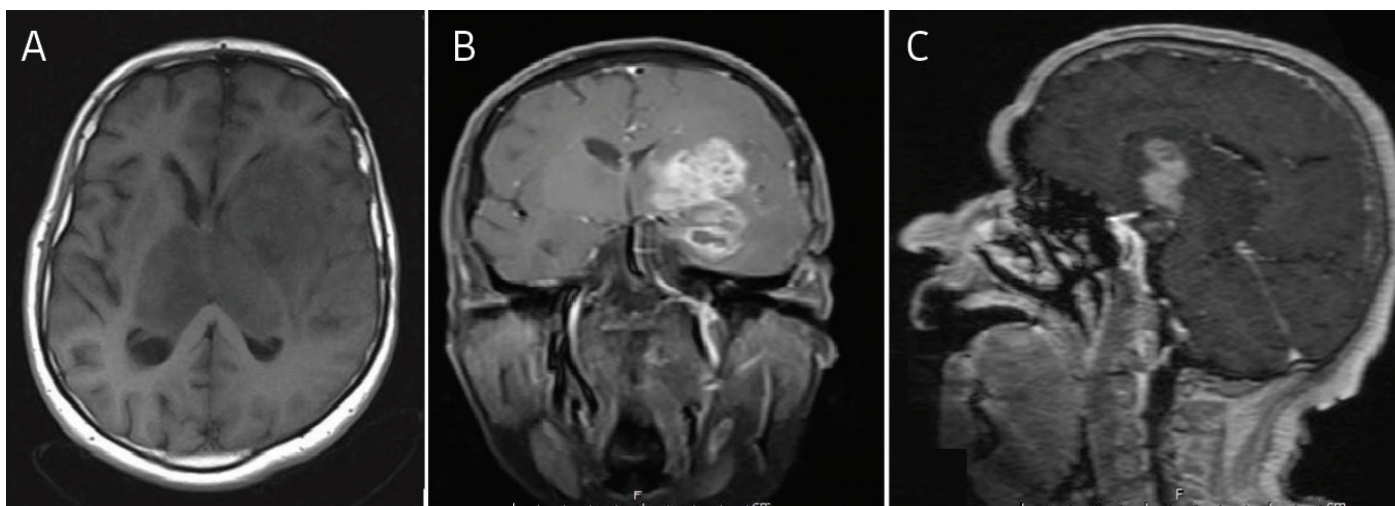


Figure 2. Contrast enhancement with gadolinium in T1 weighted (A), T1 weighted coronal, (B) and T1 weighted sagittal sections (C)

cortical tracts limit surgical access. Damage to these structures can cause much neurological impairment. On the other hand, surgical resection size is an independent factor affecting prognosis. A correlation between resected tumor volume and prognosis has been demonstrated. The aim is to resect as much as possible while paying attention to protect sensitive structures (7,8). Modalities such as MR-tractography, MR-perfusion used in preoperative planning make a significant contribution to the morbidity and prognosis due to the predetermination of the area of resection. The neuronavigation or neuroendoscopy devices used during the operation provide access to the lesion in the most convenient way. Thus, the least damage to elegant areas is aimed. Although these and similar advanced technologies are used in many clinics, novel prognostic factors related to them are not included in the literature (20,21). In our study, we investigated the relation of tumor location, which is the most important prognostic factor, with residue rates. In our study, no relation was found between tumor location and residual mass. We think that technological advances in medical equipment have reduced residual rates, especially in elegant regions. This was not consistent with the literature. One of the reasons for this is the use of advanced surgical equipment such as neuronavigation, intraoperative ultrasound, or ultrasonic aspirator before and during surgery. Thus, a safe surgical approach to these areas and maximal resection is possible.

CONCLUSION

There has been no change in the criteria to predict the survival of glioblastoma patients starting from diagnosis. New prognostic markers are needed, including pre and postoperative imaging, as well as molecular investigations. Evaluating the data used by the

clinics at standard times will make an important contribution to determine new prognostic factors.

Ethics

Ethics Committee Approval: Ethics Committee for Noninterventional Studies of our University Hospital, Bezmialem Vakıf University Faculty of Medicine (14/159).

Informed Consent: In line with the ethical rules, patient information and patient approval were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Ö., A.A., M.H.S., T.T.D., S.K., Concept: M.G.P., Design: M.G.P., Data Collection or Processing: M.G.P., E.Ö., M.H.S., Analysis or Interpretation: M.H.S., T.T.D., Literature Search: A.A., S.K., Writing: M.H.S., T.T.D.

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

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Vocal Function Following Frontolateral Laryngectomy

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Abstract

Objective: The aim of this study is to evaluate smoothed cepstral peak point and laryngostroboscopic results in patients who underwent frontolateral laryngectomy (FLL).

Methods: Eight patients who underwent FLL with bilateral modified radical neck dissection, and who completed at least 12 months of follow-up, were included. All patients underwent laryngostroboscopic evaluation at study commencement; glottal closure was examined. Voice records were taken at fundamental frequency (Fo) and smoothed cepstral peak point were analysed. Voice handicap index-10 was requested to be completed. Ten healthy individual constituted control group. Results were compared.

Results: The smoothed cepstral peak points were between 1.81-2.42 in the FLL group and 4.6-6.06 in controls, a significant difference. The Fo ranged from 61 to 192.63 Hz in the FLL group and from 118.57 to 197.61 Hz in the control group, also a significant difference. Laryngostroboscopy revealed significant differences between-group in their closure. Seven patients had incomplete closure in FLL group and the entire control group had complete closure except one female patient who had posterior glottal gap ($p=0.01$). Voice handicap index-10 results were between 31-40 in FLL group and 8-14 in control group and also revealed a significant difference.

Conclusion: FLL reduces smoothed cepstral peak point and affects the mucosal wave, reducing voice quality.

Keywords: Cepstral peak point, frontolateral laryngectomy, laryngostroboscopy, vocal quality, voice handicap index

INTRODUCTION

The aim of partial laryngectomy is to completely remove the diseased part of larynx with safe margins and to preserve function including phonation, swallowing, breathing, and stabilization (1). Modified frontolateral partial laryngectomy is a procedure which can be applied for selected early glottic carcinomas (T1 and T2) involving the anterior commissure (2). The following surgical reconstruction can be performed by bipedunculated sternohyoid muscle flap and perichondrium in order to provide bulky tissue replacing vocal folds or can be left to secondary healing (2,3). Glottic closure and the vibratory margin is an essential part of voice production. One vocal fold and an anterior commissure are removed in frontolateral laryngectomy (FLL) and reconstruction methods can be applied to replace vocal quality.

“Cepstrum is described as a discrete Fourier transform of the logarithm power spectrum; i.e. it is a log power of a log power spectrum” (4,5). The cepstral peak is the peak in the cepstrum with the highest amplitude. When a linear regression line that represents the average sound energy is drawn through the cepstrum, the distance from the cepstral peak to this linear regression line is termed the Cepstral Peak Prominence (CPP) (6). It is the measure of the degree of harmonic organization (4). Another measure is the smoothed CPP (sCPP) which represents the distance between the first harmonic peak and the point with equal frequency on the regression line through the smoothed cepstrum. The logic behind this acoustic marker is that the more periodic voice signal displays a more well-defined harmonic configuration in the spectrum (i.e., the more harmonic the spectrum), and, as a result the cepstral peak will



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be more prominent. Since it was first introduced by Hillenbrand et al. (4) and Hillenbrand and Houde (5), it has been proven to be a reliable and valid tool for evaluation of voice quality (6). It was shown that CPP integrates measures of voice waveform and periodicity perturbations, be them either amplitude, frequency or noise (7).

The vocal aspects of FLL was studied in several studies (1,3,8-10). Although voice changes were confirmed in all of the studies, there are some contradictory results (3,10). On the other hand, none of the studies evaluated sCPP in this population, this study aimed to evaluate sCPP in FLL patients.

METHODS

International review board approval was obtained from Okmeydanı Training and Research Hospital Ethical Committee (48670771-514.10). Eight patients who underwent FLL between 2010 and 2017 and completed at least 12 months of follow up was included in the study. The vocal parameters were shown not to change significantly after 12 months (11). Eight healthy individuals including 1 female, matching the age and gender were constituted as the control group.

All of the patients had laryngostroboscopic evaluation at the beginning of the study. The glottal closure was evaluated.

All voices were recorded using an AKG D5 (Vienna, Austria) dynamic microphone and a Lexicon Alpha (Lexicon by Harman, USA) external sound card. The microphone was placed 5 cm from the lips, and after deep inspiration, patients were told to sound the vowel "a" in Turkish for as long as possible. Praat software (version 4.4.13; Boersma and Weenink, University of Amsterdam, Amsterdam, the Netherlands) was used to analyse recordings and the Z-tool (James Hillebrand and Western Michigan University) was employed for sCPP analyses. Laryngostroboscopic analysis was performed by Karl Storz Pulsar 2 (Tuttingen, Germany). 70-degree rigid telescope was used. Voice Handicap Index-10 (VHI-10) which was translated and validated by Kılıç et al. (12) was used.

Statistical Analysis

The results were compared using SPSS ver. 22 software for Windows (SPSS Inc., Chicago, IL, USA). As subject numbers were limited, we employed the Mann-Whitney U test for comparisons.

RESULTS

The mean age was 55.8 ± 2.49 years in the sCPP group and 57.6 ± 4.22 years in the control group; these did not differ significantly ($p=0.83$). The sCPPs were between 1.81-2.42 in

the FLL group and 4.6-6.06 in controls, a significant difference (Table 1) (Figure 1, 2). The fundamental frequency (Fo) ranged from 182.67 to 192.63 Hz in the FLL group and from 118.57 to 197.61 Hz in the control group, also a significant difference (Table 1). Laryngostroboscopy revealed significant differences between-group in their closure. Seven patients had incomplete closure in FLL group and all of the control group had complete closure except one female who had posterior glottal gap ($p=0.01$). VHI-10 results were between 31-40 in FLL group and 8-14 in control group and also revealed a significant difference (Table 1).

DISCUSSION

T1b and T2 glottic tumors are the major indications of FLL. T2 tumors should not involve more than one-third of opposite vocal fold and may have a minimal extension to supra or subglottic regions (9). It has excellent oncological results which are comparable to radiotherapy (13). On the other hand, the vocal function is preserved and vocal folds can be replaced by bipednlicated suprahyoid muscle flap or perichondrial flap to achieve better function (9). Biacabe et al. (14) found that reconstruction resulted in better frequency and less granuloma and web formation. In contrary to this idea, Szmeja and Leszczyńska (15) concluded that scarred tissue resulted in better voice.

Our results showed that there is a significant deterioration in sCPP and VHI-10 results. As none of the patients had reconstruction, we were not able to compare reconstructed and non-reconstructed neoglottises.

So far, the evaluation of voice quality following FLL was studied in different aspects (1,3,8-10,14-17). Dedivitis et al. (10) studied the configuration of neoglottis effect on the auditory perception and found that the anterior commissure synechia caused voice quality deterioration. On the other hand, Pfuetzenreiter et al. (3) found that anterior commissure synechia did not affect results

Table 1. Results of frontolateral laryngectomy and control group

	FLL group	Control	p
sCPP	1.76 (0.44)	5.09 (0.63)	0.0009
Fo	182.67 (6.61)	148.01 (31.77)	0.0103
Glottic closure	7 incomplete 1 complete	8 complete	0.01
VHI-10	27.25 (4.30)	6 (2.72)	0.009

FLL: Frontolateral laryngectomy, Fo: Fundamental frequency, VHI-10: Voice Handicap Index-10, sCPP: Smoothed cepstral peak prominence
Mann-Whitney U test $p:0.05$ is significant



Figure 1. Smoothed cepstral analysis of frontolateral laryngectomy patients



Figure 2. Smoothed cepstral analysis of healthy subject

of acoustic voice analysis. Regardless of synechiea, signals were chaotic and aperiodic. Because of the chaotic and irregular signals, we did not perform perturbation measurements in this study. Only F_0 was evaluated and revealed a significant difference.

Cruz et al. (9) evaluated the stroboscopic data and found that 15 of the 21 neoglottis achieved complete closure. The vibration point was the glottis in 10 patients, supraglottis in 7 and mixed in 4. They also pointed out that 5 reconstructed larynx had vibration but absent in the other 5. Dedivitis et al. (16) studied with videokymography and stated that 11 of 22 patients had a vibration at the glottis, 7 had it at the supraglottis and 4 had mixed vibration source. They also said that 4 of the 11 who had glottic vibration had no closed phase. Seven patients had an incomplete glottic closure which is one of the main factors in vocal deterioration.

The most important part of our study is the calculation of sCPP which is a better indicator of voice quality in patients who underwent FLL. It does not depend on frequency and aperiodic vibration is not a handicap for sCPP. It shows the overall voice quality better than any other measurement (4-6,11). We also studied VHI-10 and found a significant difference between the groups.

The main disadvantage of our study was limited number of subjects. Moreover, none of the patients had reconstruction which prevented the comparison of it with the non-reconstructed counterpart. Because of irregular vibration pattern we did not use stroboscopic evaluation for the mucosal wave and we also did not analyze the source of vibration.

CONCLUSION

FLL reduces sCPP and causes deterioration in vocal quality. It affects both vibration and glottic closure. Further studies on larger cohorts are required to analyze not only the reconstructed but the non-reconstructed also.

Ethics

Ethics Committee Approval: Okmeydanı Training and Research Hospital Ethical Committee (48670771-514.10).

Informed Consent: Retrospective study. Approval was obtained from those who could be reached by phone.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.U., Z.S., T.L.K., G.B., Concept: Z.S., O.Ü., Design: Z.S., O.Ü., Data Collection or Processing: O.Ü., B.T., Analysis or Interpretation: Z.S., T.L.K., H.S., Literature Search: H.S.B., O.Ü., Writing: Z.S., O.Ü., G.B.

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

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The Association Between Contrast-induced Acute Kidney Injury and Neutrophil Gelatinase-associated Lipocalin

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Abstract

Objective: Neutrophil gelatinase-associated lipocalin (NGAL) has been reported as an useful marker to detect early contrast-induced acute kidney injury (CI-AKI). However most of the studies were performed in subjects taking intraarterial contrast. We aimed to evaluate the role of serum NGAL for detection of CI-AKI in patients undergoing contrast-enhanced computed tomography (CT).

Methods: We prospectively enrolled consecutive hospitalized patients with estimated glomerular filtration rate ≥ 15 mL/min/1.73m² undergoing contrast enhanced CT. Blood samples were taken before (baseline) and after 4 hours following procedure for NGAL and for serum creatinine (SCr) 12-24 hours prior to CT and again 48 hours after administration of contrast agent. The primary outcome of the study was the development of CI-AKI.

Results: A total of 70 (male, 50%) subjects with a mean age of 61.1 ± 16.1 years were enrolled. The mean baseline SCr was 1.02 ± 0.39 mg/dL. The incidence of CI-AKI was 5.7%. In the whole group serum NGAL decreased from median 119.7 (IQR, 126.3) ng/mL at baseline to median 87.3 (interquartile range, 72.9) ng/mL after contrast application. Subjects were classified into those with and without CI-AKI. Subjects with CI-AKI did not differ in baseline demographics, renal function, presence of systemic disorders and serum NGAL levels (baseline and 4 h) compared with those without CI-AKI.

Conclusion: In conclusion, 4 h measurement of serum NGAL does not seem a useful marker for the early detection of CI-AKI following IV contrast administration.

Keywords: Neutrophil gelatinase-associated lipocalin, contrast-induced acute kidney injury, contrast-enhanced computed tomography

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) also known as contrast induced nephropathy has become the third leading cause of hospital acquired AKI, because of an increasing number of patients receiving intravascular injection of iodinated contrast media every year worldwide (1). Serum creatinine (SCr) poorly reflects early changes in glomerular filtration and defines AKI before 24-48 hours (2) so considerable effort has been put into the search for new biomarkers as early indicators of AKI (3). One

of the promising biomarker is neutrophil gelatinase-associated lipocalin (NGAL).

Although renal complications associated with intraarterial contrast administration have been reported mostly, there are few studies that examined the adverse outcomes of intravenous (IV) contrast administration after computed tomography (CT) procedures.

In our study, we aimed to determine the frequency of CI-AKI among patients who underwent an IV contrast-enhanced CT and to evaluate the role of serum NGAL for detection of CI-AKI.



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METHODS

Consecutive hospitalized patients undergoing elective CT with IV contrast administration at our institution between August 2012 and March 2014 were prospectively enrolled. Exclusion criteria were age <18 years; estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m², administration of iodinated contrast media within 7 days prior to study entry; history of anaphylaxis to iodinated contrast agent; lactation; evidence of acute kidney injury defined according to the Kidney Disease Improving Global Outcomes (2); acute myocardial infarction; administration of dopamine, mannitol or theophylline prior to procedure.

Demographic and clinical data were collected from patient files. These include age, gender, weight, relevant co-morbidities such as diabetes mellitus, hypertension, coronary artery disease and malignancy, current antihypertensive medications, diuretic usage. Pre and post procedure prophylaxes based on hydration and n-acetylcysteine (NAC) therapy were done according to the decision of the physician who followed up the patients.

Blood samples were obtained for SCr from all patients 12-24 hours prior to CT and again 48 h post-procedure. SCr was measured using the creatinine enzymatic assay (Jaffe ratemethod) in the Abbott C8000 analyzer (Abbott Diagnostics, Abbott Park, IL, USA). eGFR was calculated by using (Chronic Kidney Disease (CKD) - Epidemiology Collaboration) formula (4)

Blood samples for NGAL evaluations were collected as baseline (within 1 h prior to CT imaging) and 4 h after CT imaging in ethylenediaminetetraacetic acid-anticoagulated tubes and centrifugation was carried out at 4500 cycles per minute for 10 minutes. The supernatant was separated and stored at -80°C until assayed. On study time after the samples dissolved at room temperature, NGAL levels were measured by the enzyme-linked immunosorbent assay (ELISA) technique, by using ELISA kit (Human Lipocalin-2/NGAL ELISA, number: RD191102200R @ BioVendor, Czech Republic). Subjects underwent contrast-enhanced CT were administrated of iopamidol (Iopamiro®, Santa Farma, Turkey) or iopromide (Ultravist®, Bayer, United States) (300 mg of iodine per milliliter, nonionic, monomeric, low osmolality) at doses of 1 mL per kilogram of body weight.

The primary outcome of the study was the development of CI-AKI by a rise in SCr of ≥ 0.5 mg/dL or a $\geq 25\%$ increase from baseline value, assessed at 48 hours after a radiological procedure. This is the most widely used definition of CI-AKI in the literature (5).

The protocol was approved by the Ethics Committee of Cerrahpasa Medical Faculty (number: 16285, date: 11.06.2012). The study was performed in adherence to the Declaration of

Helsinki. Informed consent was obtained from all individual participants included in the study.

Statistical Analysis

Data were expressed as mean \pm standard deviation, median, interquartile range (IQR) and frequency. Data distribution was analysed with the Kolmogorov-Smirnov test. Comparison of different parameters were done using Mann-Whitney U test whereas chi-square test or Fisher's exact test was used for categorical variables. The SPSS version of 22.0 for Windows software was used for analyses. Two tailed p value <0.05 was considered statistically significant.

RESULTS

Seventy-five patients were recruited and consented, however 5 patients did not have follow-up blood testing for SCr. A total of 70 (male, 50%) subjects with a mean age of 61.1 ± 16.1 years were enrolled. 24.3% of patients were diabetics, 40% had hypertension, 20% had malignancies, 24.3% had a history of coronary heart disease and 45.7% had infectious diseases. The mean baseline SCr was 1.02 ± 0.39 and the mean baseline eGFR was 76.7 ± 30.9 mL/min/1.73 m². Forty-eight of 70 subjects (68.6%) had a baseline eGFR of ≥ 60 mL/min/1.73 m². The hydration and NAC therapy according to patient's status and clinician's decision were given to 61.4% and 47.1% of patients, respectively. The incidence of CI-AKI was 5.7%. Baseline demographic and clinical data of the study subjects grouped based on eGFR as <60 mL/min/1.73 m² and ≥ 60 mL/min/1.73 m² are shown in Table 1. Patients with eGFR as <60 mL/min/1.73 m² received significantly more hydration therapy before contrast procedure and used significantly more diuretic drugs than patients with eGFR as ≥ 60 mL/min/1.73 m².

In the whole group serum NGAL decreased from median 119.7 (IQR, 126.3) ng/mL at baseline to median 87.3 (IQR, 72.9) after contrast application. Twenty-six patients (37.1%) had a rise [median: 14.3 (IQR, 34.7) ng/mL] in serum NGAL levels after CT imaging. For NGAL levels between baseline and after contrast exposure, we found a rise of 25% in 15 patients, a rise between 25-50% in 6 patients and a rise over 50% in 5 patients. In Figure 1 serum NGAL levels at baseline and 4 h with diagnosis of CI-AKI is shown as a logarithmic scale.

Based on the primary outcome, subjects were classified into those with and without CI-AKI. Then we compared demographic characteristics (age, gender, weight), baseline renal function, presence of systemic disorders and serum NGAL levels (baseline and 4 h) between patients with CI-AKI (n=4) and patients

Table 1. Baseline characteristics and demographic data according to baseline estimated glomerular filtration rate levels of patients undergoing contrast-enhanced computed tomography

Variable	All Patients n=70	eGFR <60 mL/min/1.73 m ² n=22	eGFR ≥60 mL/min/1.73 m ² n=48	p value
Age, year	61.1±16.1	72.9±9.3	55.7±15.8	0.000
Male, n (%)	35 (50)	8 (36.4)	27 (56.3)	0.122
Weight, kg	70.2±13.6	73.5±16.7	68.8±11.8	0.183
Diabetes mellitus, n (%)	17 (24.3)	7 (31.8)	10 (20.8)	0.320
Hypertension, n (%)	28 (40)	12 (54.5)	16 (33.3)	0.093
Coronary artery disease, n (%)	17 (24.3)	8 (36.4)	9 (18.8)	0.111
Malignancy, n (%)	14 (20)	5 (22.7)	9 (18.8)	0.699
Infectious diseases, n (%)	32 (45.7)	11 (50)	21 (43.8)	0.626
ACE inh/ARBs usage, n (%)	11 (15.7)	4 (18.2)	7 (14.6)	0.701
Diuretic usage, n (%)	15 (21.4)	9 (40.9)	6 (12.5)	0.007
Hydration therapy, n (%)	43 (61.4)	19 (86.4)	24 (50)	0.004
NAC therapy, n (%)	33 (47.1)	14 (63.6)	19 (39.6)	0.061
eGFR _{baseline} , mL/min/1.73 m ²	76.7±30.9	42.4±10.8	92.5±23.4	0.000
SCr _{baseline} , mg/dL	1.02±0.39	1.44±0.34	0.82±0.24	0.000
NGAL _{baseline} , ng/mL	119.7 (126.3)	120.9 (111.9)	113.9 (162.8)	0.548
SCr 48 h, mg/dL	0.96±0.39	1.36±0.34	0.88±0.24	0.000
NGAL 4 h, ng/mL	87.3 (72.9)	100.6 (62.5)	86.6 (113.3)	0.752
Acute kidney injury, n (%)	4 (5.7)	2 (9.1)	2 (4.2)	0.585

ACE inh: Angiotensin converting enzyme inhibitor, ARBs: Angiotensin receptor blockers, NAC: N-acetyl cysteine, eGFR: Estimated glomerular filtration rate, SCr: Serum creatinine, NGAL: Neutrophil gelatinase-associated lipocalin

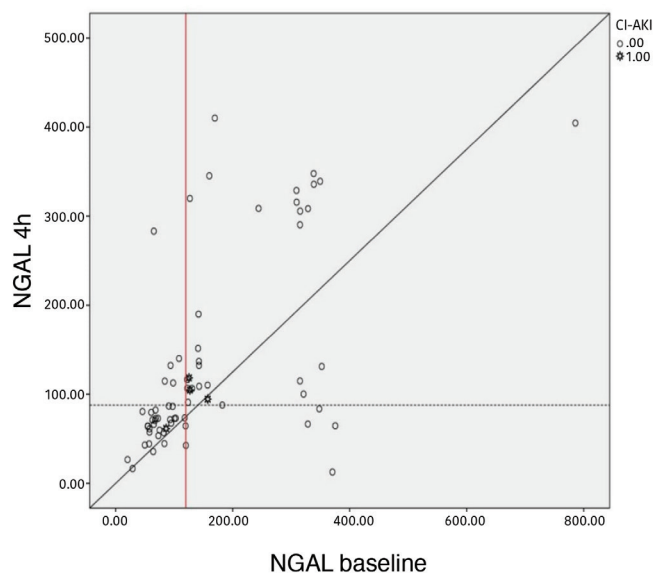


Figure 1. NGAL and CI-AKI diagnosis on a logarithmic scale. Dotted line: median level of serum NGAL 4 h, red line: Median level of baseline serum NGAL
 NGAL: Neutrophil gelatinase-associated lipocalin, CI-AKI: Contrast-induced acute kidney injury

without CI-AKI (n=66). No significant differences were noted in studied variables (data were not shown). In Table 2, association of baseline serum NGAL levels with clinical variables was shown. Baseline serum NGAL was not found significantly associated with any clinical variable.

DISCUSSION

The frequency of CI-AKI in our patients undergoing IV contrast-enhanced tomography was 5.7%. The reported frequency of CI-AKI is 1-2% in patients with normal renal function, but increases up to 25% in patients with risk factors for instance the combination of CKD and diabetes, congestive heart failure, advanced age, and concurrent use of nephrotoxic drugs (6). By contrast to that associated with angiography, the risk of CI-AKI associated with contrast enhanced CT scans is quite low, even among patients with CKD (7,8). Filiopoulos et al. (9) found CI-AKI in four subjects (8.5%) in a population who underwent contrast enhanced CT and had well-preserved renal function. In another study, Weisbord et al. (8) found the frequency of AKI as 3.5% in patients with eGFR less than 60 mL/min/1.73m² undergoing elective contrast-enhanced CT. In addition three recent

Table 2. Association of baseline serum NGAL levels with clinical variables

Variable	Baseline NGAL (ng/mL) Median (IQR)	p value
Gender		
Female	119.9 (162.2)	0.925
Male	108.3 (115.1)	
Age, years		
≤74	120.7 (130.3)	0.572
>74	118.9 (186.1)	
Diabetes mellitus		
Yes	126.8 (155.7)	0.742
No	108.3 (144.9)	
Hypertension		
Yes	120.9 (198.9)	0.514
No	110.3 (132.5)	
Coronary heart disease		
Yes	119.5 (59.1)	0.598
No	119.9 (210.1)	
Infectious diseases		
Yes	113.0 (106.5)	0.782
No	120.9 (189.1)	
Malignancy		
Yes	111.3 (105.5)	0.971
No	120.7 (159.2)	
SCr _{baseline} , mg/dL		
<1	113.1 (117.8)	0.348
≥1	119.7 (195.0)	
eGFR _{baseline} , mL/min/1.73 m ²		
<60	120.9 (111.9)	0.548
≥60	113.9 (162.8)	

NGAL: Neutrophil gelatinase-associated lipocalin, SCr: Serum creatinine, eGFR: Estimated glomerular filtration rate, IQR: Interquartile range

prospective trials involving contrast enhanced CT with eGFR less than 60 mL/min/1.73m² found an overall incidence of CI-AKI, of approximately 5% (10-12). Interestingly, Muratoglu et al. (13) found CI-AKI as 16.2% in their study patients with no history of any renal disorder undergoing CT with contrast.

We know that SCr is not an optimal biomarker of kidney function and a change of SCr within 48 hours after contrast media injection might result in a delay for diagnosis CI-AKI. Over 50% of kidney function must be lost before SCr begins to rise (14). Early detection of CI-AKI after contrast media exposure is important for appropriate intervention and prevention of the progress of renal impairment. So considerable effort has been put into the

search for new biomarkers as early indicators of AKI.

NGAL is a 25-kDa protein produced by renal tubular cells in response to different types of injury (15). NGAL has been proved as an early, sensitive, non-invasive biomarker for AKI in different clinical settings such as in cardiac surgery (16,17), critical care (18,19), and kidney transplantation (20,21). Also it has been shown to be useful for earlier diagnosis in patients who underwent cardiac surgery and/or any procedure with intraarterial iodinated contrast material administration (22,23). In a recent meta-analysis; NGAL level has been found as a valuable renal biomarker for predicting CI-AKI in patients who undergo percutaneous coronary intervention or coronary angiography (24). However; its performance in patients undergoing contrast-enhanced CT is unclear.

Firstly Mishra et al. (25) reported a significant rise in serum and urinary NGAL in samples taken as early as 2 h after cardiopulmoner bypass surgery in children who developed acute renal injury. They also found a small but significant rise in samples taken similarly after the same procedure in children who never developed acute renal injury. The cause of this rising was believed to be the result of NGAL release in the bloodstream secondary to inflammatory activation of neutrophils. In another study, Bachorzewska-Gajewka et al. (26) also demonstrated significantly high NGAL levels in patients with CI-AKI starting 2 h (serum NGAL) or 4 h (urinary NGAL) after percutaneous coronary intervention. Similarly McCullough et al. (27) found that serum NGAL began to rise in plasma approximately 6 h after contrast exposure in parallel with a rise in SCr in subjects with eGFR <75 mL/min/1.73 m² who underwent non-urgent coronary angiography. Alharazy et al. (28) had reported that serum NGAL at 4 hours did not change significantly in patients with stable CKD stages 2 to 4 who underwent coronary angiography then they found significant increase in serum NGAL at 24 hours and in SCr at 48 hours. Surprisingly, in 62.9% of our patients the concentrations of serum NGAL dropped after contrast application. Similarly to our study; Ribitsch et al. (29) found that only ten patients (1.62%) undergoing intra-arterial angiography showed a significant rise of urinary NGAL and of whom one developed CI-AKI. They found decreased NGAL levels in parallel with urine osmolality so they suggested a diluting effect might be considered. According to meta-analysis recently published by Wang et al. (24), they hypothesized that the differences between these studies might be attributed to the dilution caused by adequate hydration however the hydration regimen has not been reported in most studies.

We know that there are major differences in patient populations, contrast volume administrated and intra-procedural

complications between the two settings; contrast-enhanced CT and percutaneous coronary interventions. In Table 3, studies evaluating performance of NGAL predicting CI-AKI in patients undergoing contrast-enhanced CT. Firstly V. Filiopoulos et al. (9) demonstrated that plasma NGAL 6 h after contrast administration appeared to be a useful biomarker in the early prediction of CI-AKI in patients undergoing contrast-enhanced CT. Also Lacquaniti et al. (15) had reported that Scr levels showed a statistically significant increase 48 hours postcontrast whereas serum and urinary NGAL were early markers with their elevations observed after only 8 hours in their patients with stable stage 3 CKD undergoing CT with administration of iomeprol (AUC=0.995 and 0.992 for serum and urine NGAL, respectively). Muratoglu et al. (13) demonstrated that serum NGAL level increased at the 6 h and decreased at the 72 h in patients undergoing contrast-enhanced with CI-AKI (AUC=0.98). Our findings contrast these findings.

One major point of this new biomarker may be the fact that only little is known about predictive pattern or cut-off value in patients with underlying several co-morbidities such as inflammation, chronic heart disease, diabetes and CKD. Several investigators discovered a significant inverse relation between NGAL and renal function defined by eGFR (30). Because of the differences in the initial renal function, there is no effective method for integrating cut-off values (24). Ribitsch et al. (29) showed in their cohort that baseline urine NGAL levels were significantly associated with diabetes, lower GFR, cystatin C, proteinuria, age and female sex. However in our study, we did not find any association with baseline serum NGAL level and clinical variables.

Our study had some limitations. An important limitation is few sample size and the very few cases with CI-AKI (n=4). A larger study population could make the results more reliable. According to previous studies as indicated before, mostly plasma NGAL appeared to be no sooner than 4 h after contrast exposure so serial measurements would have been valuable. A large number of CI-AKI cases will be needed with blood NGAL measurements to determine the risk.

CONCLUSION

In conclusion, 4 h measurement of serum NGAL does not seem a useful marker for the early detection of CI-AKI following IV contrast administration.

Ethics

Ethics Committee Approval: Ethics Committee of Cerrahpasa Medical Faculty (number: 16285, date: 11.06.2012).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Surgical Treatment of Humeral Shaft Fractures by Arthroscopy-assisted Intramedullary Nail Fixation

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Abstract

Objective: Humeral shaft fractures face with controversies about the entry site of intramedullary nailing (IMN) due to its potential complications. We aimed to evaluate feasibility of arthroscopy-assisted intramedullary nail fixation for the management of these fractures with respect to its mid-term clinical and functional outcomes, complication rates of nail entry site, and fluoroscopy duration.

Methods: We examined medical data of 21 patients who underwent arthroscopy-assisted IMN after closed reduction upon diagnosis of humeral shaft fracture. Analyzed parameters included duration of anesthesia, surgery, fluoroscopy, preoperative hospitalization, and union; surgical complication rates; and the degree of lateralization between ideal and applied nail entry site, as measured by shoulder computed tomography scans. Shoulder functions were assessed by Constant and American Shoulder and Elbow Surgeons (ASES) scoring.

Results: Patients were found to be followed up for a mean of 22.8±4.76 months. The mean duration of surgery was 56.9±14.27 minutes. The mean fluoroscopy time was detected as 1.63±0.49 minutes. Distal locking was performed without fluoroscopy (electromagnetic targeting or internal locking nail) in 15 patients and with free hand method under fluoroscopy in six patients. The mean duration of fluoroscopy in these techniques were 1.47±0.41 minutes and 1.91±0.52 minutes, respectively. No patient was found to have subacromial impingement syndrome. The mean lateralization of nail entry sites was measured as 0.61±0.73 mm. The mean degree of varus was 2.38±1.18. The mean ASES and Constant scores were found as 89±2.81 and 90±4.59 points, respectively. Excellent/good functional outcomes had been reported by 90.5% of the study population.

Conclusion: Arthroscopy-assisted technique may minimize rotator cuff injury and thereby may provide satisfactory outcomes in postoperative shoulder functions. This technique may be a feasible and safe option associated with reduced entry site complications and potentially less exposure to radiation from shorter use of fluoroscopy.

Keywords: Humerus, shaft, fracture, arthroscopy-assisted, intramedullary nail, antegrade

INTRODUCTION

Humeral shaft fractures constitute 5-8% of all extremity fractures with an annual incidence of 13/100.000. These fractures are managed with either conservative or surgical approaches (1). While the former includes functional bracing, spica cast, Velpeau bandage, and coaptation splint; surgical approaches are plate-screw fixation, intramedullary nailing, and external fixator (1,2).

In humeral fractures, antegrade intramedullary nailing (IMN) has the advantages of minimally invasive fashion, rapid fracture healing, lower iatrogenic radial nerve damage. On the other hand, it might also cause long-term shoulder dysfunction after injury to rotator cuff and cartilage at the entry site. The fact that the proximal nail may stay within the joint could impair shoulder functions due to subacromial impingement and rotator cuff



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irritation, increasing the need for nail removal. Other drawbacks of intramedullary nails include iatrogenic fractures during IMN and radiation exposure due to fluoroscopy (3-5).

In this study, we aimed to evaluate feasibility of the arthroscopy-assisted IMN of the humerus in terms of entry site complications and duration of fluoroscopy.

METHODS

After obtaining approval from local ethics committee (Okmeydanı Training and Research Hospital 19.12.2017-789), medical records of 21 patients who underwent arthroscopy-assisted antegrade humeral IMN fixation upon surgical indication due to the diagnosis of humeral shaft fracture between January 2015 and September 2017 were retrospectively reviewed in this study. Informed consent was obtained from all individual participants included in the study. Included patients had to have clinical and radiological documentation of humeral diaphyseal fracture where the surgery was indicated with following criteria: shortening of >3 cm, $>30^\circ$ angulation at coronal plane, and $>20^\circ$ angulation at sagittal plane. Patients with open epiphyseal lines at the proximal humerus, infected fractures, Gustilo-Anderson type 3 open fractures, multiple fractures, and fractures where open reduction was performed were excluded.

Medical data of the patients were collected by reviewing medical records, operating room records, arthroscopy and fluoroscopy image recordings, plane X-ray and computed tomography images taken during outpatient visits, and physician- or patient-reported shoulder functions as assessed by Constant and ASES scores.

Implanted nails were belonged to two different companies. Fourteen patients had been implanted Trigen humeral nail of Smith and Nephew. Six of these patients underwent nailing by distal locking under fluoroscopic guidance with free hand method. For the remaining eight patients, distal locking was performed without fluoroscopy by using electromagnetic targeting (Smith and Nephew-Sureshot). Seven patients had been implanted TST's InsafeLock humerus nail. Distal locking of this nail was performed via using elastic, threaded pin system which was advanced through the nail. Fluoroscopy was not used for distal locking in these patients.

Surgical Technique

Intravenous cefazolin prophylaxis was administered for a total of 24 hours with the initial dose one hour before the surgery. All patients were prepared in lawn chair position under general anesthesia. Fluoroscopy device and arthroscopy tower were positioned to be suitable for surgery. Following the essential sterilization and covering procedures, anatomic markers and fracture line were determined with marker pen on the side to be operated. The surgery was started with the incision performed through the inferomedial and posterior of the lateral edges of the spine of scapula, through which posterior arthroscopic port was inserted to visualize the joint. In order to determine the entry site of the nail, a 2.2 mm Kirschner wire was introduced percutaneously over the joint cartilage about 20 mm medial to the greater tubercle posterior to the biceps tendon (1.5 cm distal to the anterolateral border of the acromion) under the guidance of fluoroscopy, targeting humeral shaft and intramedullary cavity (Figure 1).

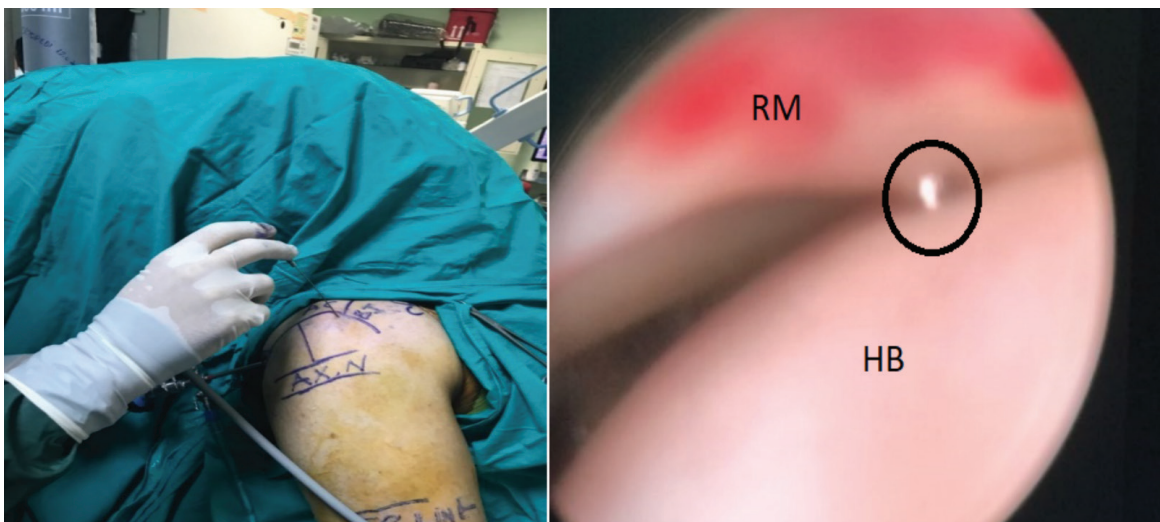


Figure 1. Percutaneous insertion of the guidewire after identifying the entry site (left) and arthroscopic image of the inserted guidewire to the entry site (right)

HB: Humeral head, RM: Rotator cuff

After arthroscopic and fluoroscopic verification, a mini skin incision of approximately 2 cm was made at the level of the K-wire. Deltoid fibers were passed through blunt dissection to reach at the supraspinatus muscle. Supraspinatus muscle was separated by a 10 mm incision which was parallel to its tendon's extension. A cannulated drill was sent over K-wire to the proximal humerus. One guidewire was sent from the drilled part to pass through the fracture line. After fracture reduction was confirmed under fluoroscopy; humeral medulla was reamed with flexible-bendable reamers. Afterwards, intramedullary humeral nail was inserted in appropriate diameter and length.

After arthroscopically ensuring that the proximal part of the nail was embedded to the joint cartilage, not leading to subacromial impingement, the proximal nail was locked by two screws delivered over the external guide. The heads of these screws were arthroscopically confirmed not to penetrate the joint cartilage (Figure 2A). In patients where internal locking nail had not been used, distal locking was performed with two screws via mini incision (with or without fluoroscopy depending on the brand/model of the nails used). Top screw was inserted under arthroscopic guidance. Finally, it was ensured that the proximal part of the nail was not within the joint cavity (Figure 2B). Afterwards, supraspinatus muscle was repaired with an unabsorbable suture followed by suturing of the skin. The joint was irrigated through arthroscopic port to eliminate intraarticular debris before the arthroscopic entry site was closed with unabsorbable suture, and the surgery was terminated.

Statistical Analysis

The suitability of the data to the normal distribution was tested with Shapiro-Wilk test, Student's t-test was used for comparison

of features with normal distribution in 2 independent groups, and Mann-Whitney U test was used for comparison of normal distribution with 2 independent groups. The variables with categorical measurements were analyzed by Pearson and Fisher's exact chi-square tests. Descriptive statistics are given as mean \pm standard deviation for numerical variables and number and % values for categorical variables. SPSS Windows version 24.0 package program was used for statistical analysis and $p < 0.05$ was considered statistically significant.

RESULTS

The study included 11 male and 10 female patients. The mean age was found to be 70.66 ± 17.5 years. The mean follow-up period was 22.8 ± 4.76 months. The mechanisms of injury showed the most common etiology to be the fractures occurring after simple fall in 13 patients. One patient (4.7%) had preoperative radial nerve deficit which was improved during the follow-up. One patient had superficial wound infection in the postoperative period and treated with intravenous antibiotics.

The fractures of the patients were grouped according to AO fracture classification, where four different fracture types were determined. The distribution of the groups was determined as nine patients for A1, six patients for A2, and three patients for each of A3 and B1.

The mean preoperative duration was detected as 3.19 ± 1.83 days. The mean duration of the surgery and anesthesia was 56.9 ± 14.27 minutes and 82.57 ± 14.44 minutes, respectively. The mean time for union was found as 18.12 ± 3.01 weeks.

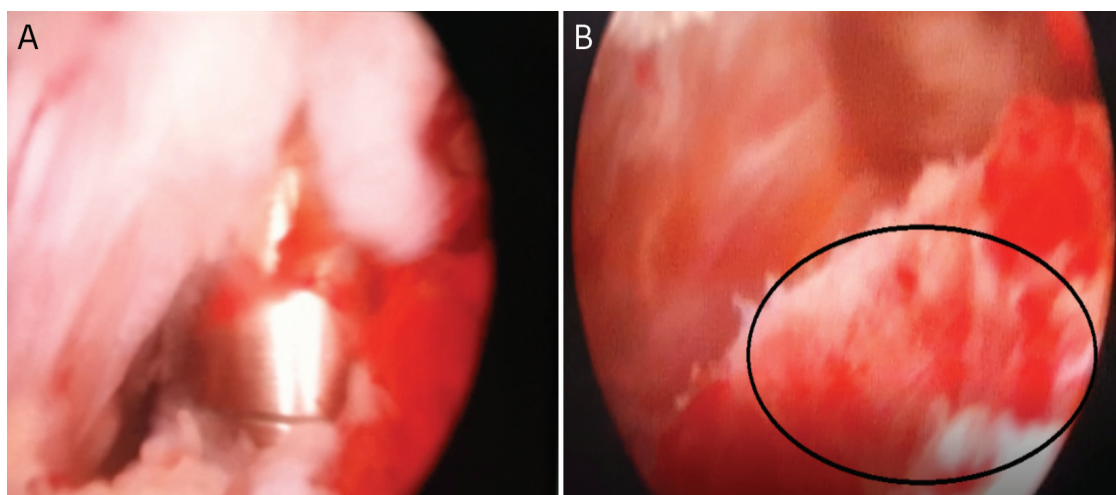


Figure 2. A) In arthroscopic view, the nail was inserted into the humerus. The line on the image belonged to the external guide, showing that the nail was completely within the joint (left). B) The black ring showed the entry site of the nail postoperatively, with the nail completely inside the joint, in arthroscopic view (right)

One patient was found to be operated due to delayed union after conservative approach. Twenty patients underwent surgery due to primary fracture. Distal locking was performed without fluoroscopy in 15 patients and with free hand method under fluoroscopy in six patients. The mean duration of fluoroscopy in these techniques were 1.47 ± 0.41 minutes and 1.91 ± 0.52 minutes, respectively; while the overall duration of fluoroscopy was 1.63 ± 0.49 minutes.

No patient was found to have subacromial impingement syndrome due to positioning of the proximal nail superior to the level of cartilage surface. The mean length of lateralization between ideal and applied nail entry site, as measured by shoulder computed tomography axial images, was 0.61 ± 0.73 mm. No patient was found to develop valgus deformity after reduction. The mean degree of varus was $2.38^\circ \pm 1.18^\circ$. The mean antero-posterior angulation was $2.54^\circ \pm 1.22^\circ$. The mean ASES and Constant scores were found as 89 ± 2.81 and 90 ± 4.59 points, respectively. Constant scoring was detected to reveal excellent/good functional outcomes in 90.5% of the study population.

The effects of the distal locking performed with free hand method or without fluoroscopy on total fluoroscopy time were also compared. There was no significant difference between the two methods ($p=0.107$). There was also no statistically significant difference between distal locking methods in terms of the duration of the surgery ($p=0.482$). The mean time of fluoroscopy was determined to be longer in AO type A3 fractures than that in AO type A1, type A2, and type B1 fractures. The association between the mean length of lateralization of the entry site and the mean degree of postoperative varus was found as statistically significant ($p=0.005$) and Pearson test showed positive correlation ($r=0.351$), (Figure 3).

DISCUSSION

A major disadvantage of the intramedullary nails is the need for fluoroscopy, which poses a risk for surgeons and other operating room staff during the surgical procedure (6). Mean times of fluoroscopy used in IMN vary between 2-4.6 minutes in humeral fractures (6-8). Franck et al. (9) in their study with expandable humerus nailing, reported the mean duration of fluoroscopy to be 1.5 minutes, concluding it to be very short while proximal and distal locking were not performed. In our study, the mean duration of fluoroscopy used during the surgery was 1.63 minutes. In order to determine nail entry site, to drill its proximal part, and to ensure whether proximal nail and proximal locking screws penetrate the joint during arthroscopy-assisted humeral nailing, using a camera might decrease the need for fluoroscopy.

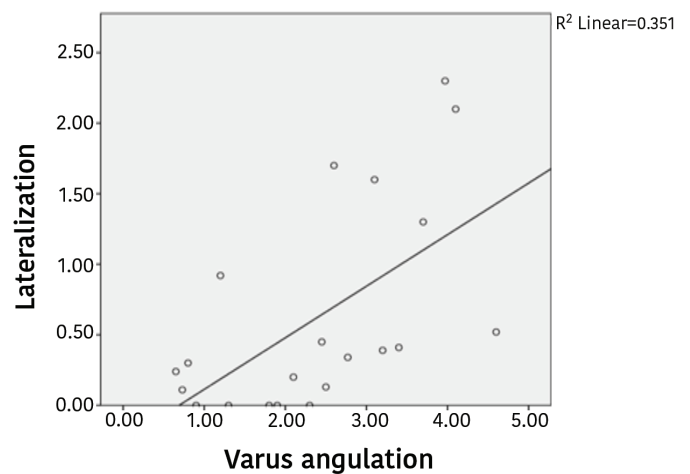


Figure 3. The association between the degree of postoperative varus and the length of lateralization of the nail on CT axial images
CT: Computed tomography

In this context, arthroscopy-assisted IMN may be associated with reduced radiation exposure to the operating room staff and the patient.

Fluoroscopy-guided locking techniques applied during distal locking of intramedullary nails also substantially prolong the surgery time and increase the amount of radiation being exposed. The duration of fluoroscopy can be reduced by using electromagnetic targeting during distal locking (10). The mean fluoroscopy time of 15 patients to whom distal locking was performed without fluoroscopy was 1.47 minutes, compared to that of 1.91 minutes in those to whom distal locking was performed with free hand method; where no significant difference was found. On the other hand, AO types A3 fractures were determined to have significantly prolonged fluoroscopy than that in other types of fractures. We partly attribute the lack of the differential effect of distal locking methods on fluoroscopy time to potential two factors. First, the failure to record the fluoroscopy duration in those where only distal locking was performed did not allow us to make a statistical comparison in fluoroscopy time. In addition, fracture types influenced the fluoroscopy time in varying degrees. We suggest that incorporation of fluoroscopy-free distal locking to the arthroscopy-assisted IMN could further reduce radiation exposure.

Several studies reported mean duration of surgery in antegrade humerus nailing to vary between 50.8 to 78 minutes (2,3,6-8,11,12). In our study, we determined that the average duration of surgery was 56.9 minutes. It might be suggested that arthroscopy, as an additional procedure to standard antegrade nailing, may not be associated with prolonged operation time during arthroscopy-assisted IMN.

The incidence of iatrogenic greater tubercle fractures during antegrade nailing is 2-11%. It occurs when the entry site of the rigid nail remains at the lateral. During nailing, while the tip of the nail is based on the medial cortex of the humerus, the nail makes a pressure on the lateral cortex of the humerus due to the leveraging effect of the acromion; which may result in fractures of the greater tubercle (3,8). In our study, no iatrogenic tubercle fracture was detected. Mean length of lateralization between the ideal and applied nail was measured as 0.61 mm, where the nails appear to be inserted to the proper position with a likely negligible deviation. Arthroscopic technique may provide the benefit of accurate identification of the entry site by direct visualization, which might be associated with the prevention of intraoperative greater tubercle fractures.

IMN of the humerus may be complicated with varying degrees of varus angulation that may cause functional impairment (3). Primary malalignment is largely the result of an unsuitable entry site or a fracture site malreduction (13). A nail insertion from the correct entry point should automatically ensure cortical alignment of the fracture (14). In our study, anteroposterior and lateral radiographs of the patients did not show valgus. On the other hand, angulations found at coronal (2.38°) and sagittal (2.54°) planes could be regarded as negligible in cosmetic and functional aspects. This could be explained by correct positioning of the nails to entry sites in all patients. Arthroscopy-assisted IMN might be associated with reduced rates of primary malalignment due to the inappropriate nail entry sites (Figure 4).

The duration of union after antegrade nailing ranged between 6.7 weeks to 13.9 weeks (2,6,15). In our study, the mean union time was 18.12 ± 3.01 weeks, which seem to be several weeks longer than those reported in the literature. In our study, 61.9%

of the patients had fractures after simple falls and the mean age was 70.66 years. We attribute prolonged union detected in our study partly to advanced age and osteoporosis.

Remaining of the proximal of the nail under or within the rotator cuff has been associated with several complications, including shoulder pain and subacromial impingement (3,16). Baltov et al. (3) reported shoulder complaints and delay in resuming shoulder and usual arm functions in 7.2% of their cases secondary to positioning of the proximal nail within the joint. They also reported subacromial impingement due to insufficient embedment of the nail in 10.8% of patients, and shoulder problems due to compression caused by the head of the proximal locking screw in 4.5%. The authors also reported the need for additional surgical procedures for these problems. In our study, no proximal part or proximal locking screw of the nail was within the joint. We believe that arthroscopy-assisted IMN may be associated with reduced rates of the subacromial impingement owing to direct joint visualization.

Fan et al. (2) reported mean Constant score as 90.2 and ASES score as 90.4 in their IMN patients. Campochiaro et al. (17) reported mean Constant score as 90.6 points, which they suggested as very satisfactory. Rajagopal et al. (18) found mean Constant score as 90.5 points, and reported excellent-good outcomes in 95% of their patients. The mean ASES score was reported 93.3 points by these investigators. Several factors could yield better should functions by reducing rotator cuff-related problems and iatrogenic shoulder pain: use of a medial entry site away from the avascular region of the rotator cuff, a delicate surgical dissection, a thorough embedment of the nail into the humerus, gentle progressive drilling, correct entry point, minimal injury to the rotator cuff, proper insertion of the nail tip, and removal of

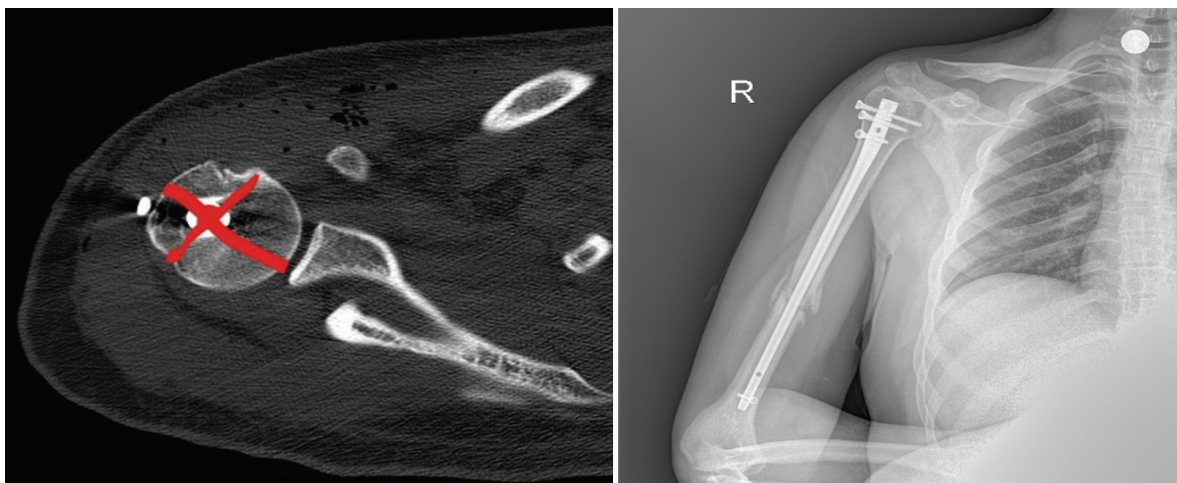


Figure 4. Axial section of the computed tomography of a patient in the postoperative period showing that the nail is at the appropriate insertion point, marked with an “X” (left). The postoperative X-ray of the same patient, where the varus was measured as 0.63° (right)

the intraarticular debris (18,19). In our study, the mean Constant score was 90 points and 90.5% of patients had excellent-good functional outcomes. On the other hand, the mean ASES score was 89. In light of these findings, arthroscopy-assisted IMN could provide several advantages such as reduced rotator cuff injury during humeral drilling and nail insertion, accurate entry point, irrigation and removal of intraarticular debris postoperatively, and lack of rotator cuff irritation by the nail; which might be associated with sufficient level of shoulder functions and reduced need for physical therapy postoperatively.

Axillary nerve deficit due to long proximal skin incision is also a rare complication of antegrade nailing reported in the literature (20). In our study, no axillary nerve damage was observed. The surgical incision in arthroscopy-assisted IMN is short enough for the nail to pass and ends far away from the axillary nerve level, which could prevent against any potential axillary nerve injury.

Arthroscopy has been reported have several complications, including the risk of intraarticular and extraarticular infections, respiratory problems due to fluid extravasation, skin necrosis, neurovascular damage, iatrogenic tendon and deltoid injury, shoulder rigidity, and chondrolysis (21-23). In our study, we did not detect any complications related to shoulder arthroscopy. Considering that arthroscopy-assisted IMN is a combined procedure that incorporates antegrade humeral nailing and shoulder arthroscopy, the possibility of the complications pertaining to the latter will always exist, which might be regarded as a drawback.

The shortcomings of the study were retrospective and the fact that arthroscopy-assisted nailing could not be compared with standard antegrade intramedullary nailing. In addition, the only missing part is that the fluoroscopy times cannot be recorded and compared during distal locking.

CONCLUSION

It appears that arthroscopy-assisted technique has the potential to minimize rotator cuff injury compared to the conventional antegrade approach, which in turn, provides satisfactory outcomes in postoperative shoulder functions. It may further reduce entry site complication rates and radiation exposure from the use of fluoroscopy. Therefore, we believe arthroscopy-assisted IMN to be a feasible and safe method for humeral shaft fractures.

Ethics

Ethics Committee Approval: Okmeydanı Training and Research Hospital 19.12.2017-789.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.G., Y.I., A.Y., Design: A.Y., C.D.B., Analysis or Interpretation: A.Y., H.G., Y.I., Literature Search: A.Y., C.D.B., T.O.B., Writing: A.Y., S.S.D., M.A.

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

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Results of Open Reduction and Internal Fixation in Calcaneal Fractures

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Abstract

Objective: We aimed to evaluate the clinical and functional outcomes of 45 patients who underwent open reduction and internal fixation for calcaneal fractures.

Methods: Sanders classification system was used to determine the fracture type. American Orthopaedic Foot and Ankle Society (AOFAS) hindfoot scale was used for clinical evaluation of patients. The patients were hospitalized with Jones bandage-like bandage or short leg splint. The patients were treated with ice, elevation, parenteral nonsteroidal anti-inflammatory drugs and thromboembolism prophylaxis. All of the patients were evaluated with wrinkle test at their visits. Those who were positive for wrinkle test were operated on a mean of 14.3 days (1-25). Four of the patients had minimally invasive surgery and 41 of them were operated with extended lateral intervention. The mean follow-up period was 25.8 months (8-56 months). After discharge, the patients were called for routine follow-up visits every 15 days, then monthly checks in the first 1.5 months, then every 3 months after the 6th month and yearly after the 1st year.

Results: Nine of 45 patients were female (20%) and 36 were male (80%). The mean age of the patients was 39.9 (21-60) years. Preoperatively, the mean Böhler angles were 3.6° and the Gissane angles were 128.8. The mean AOFAS score was 83.9. According to the fracture type; this was 94.6 in patients with tongue fractures, 88 in type 2 patients, 82.8 in type 3 patients and 78.3 in type 4 patients.

Conclusion: As a result of this study good and satisfactory results can be obtained radiologically and functionally in Sanders type 2, type 3 and tongue type fractures. However, although we obtained radiologically good results in Sanders type 4 fractures, we did not achieve functional excellent results in any patients.

Keywords: Calcaneus, fracture, Sanders, open reduction, internal fixation

INTRODUCTION

Calcaneus is the most common fracture of the tarsal bones. 75% of these fractures are intra-articular fractures. Etiologically, it is caused by high-energy injuries such as falls from high altitudes and traffic accidents, and other pathologies can be seen. The aim of the treatment is anatomical reduction of the subtalar, calcaneocuboid joints and to provide the length, width, height and valgus position of the calcaneus. In this study, we aimed to evaluate the results of the patients who underwent internal fixation in our clinic between 2010 and 2015 with current and literature information.

METHODS

In our study, 63 patients who underwent internal fixation after calcaneus fracture between January 2010 and February 2015 Okmeydanı Training and Education Hospital Orthopedics and Traumatology Clinic were evaluated. Fifty fractures of 45 patients who could be reached or reached at their final controls were included in the study.

Nine of 45 patients were female (20%) and 36 were male (80%). The mean age of the patients was 39.9 (21-60) years. Seven of the patients were open fractures (15%) and the rest were closed



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fractures (85%). One of the fractures was caused by gunshot wounds and the others as a result of falling from a height. One patient had lateral malleolar fracture, two had tibial plateau fracture, two had distal radius fracture, three had vertebral fracture, two had tibial pilon fracture. Five (13.3%) patients had bilateral involvement, 17 (34%) had left side and 33 (66%) had right side. Two patients had insulin dependent diabetes, one patient had cold urticaria, one patient had aortic valve insufficiency and one patient had epilepsy. All patients with bilateral fractures underwent open reduction and internal fixation.

Standard ankle AP and lateral radiographs were taken in all patients following the first emergency intervention. Computed tomography (CT) scans with axial, sagittal and coronal sections were used for calcaneus fracture classification. Sanders classification system was used to determine the fracture type (1). Accordingly, 3 patients were tongue type, 10 patients were type 2, 27 patients were type 3 and 10 patients were type 4. Distributions according to fracture type were shown in Figure 1. The patients were hospitalized with Jones bandage-like bandage or short leg splint. The patients were treated with ice application, elevation, parenteral nonsteroidal anti-inflammatory drugs and thromboembolism prophylaxis. All of the patients were evaluated with wrinkle test at their visits. Those who were positive for wrinkle test were operated on a mean of 14.3 days (between 1-25 days). Four of the patients had minimally invasive surgery and 41 of them were operated with extended lateral intervention.

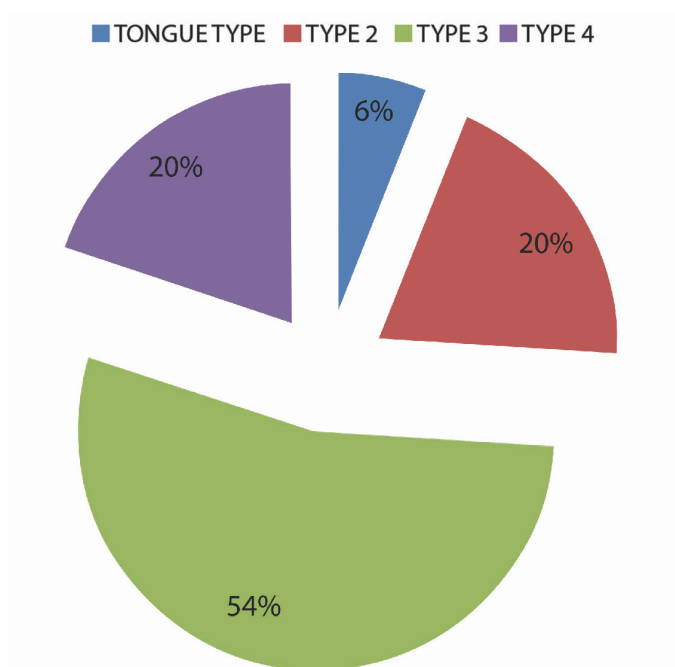


Figure 1. Sander classification of fractures

After the reduction was achieved, the bone cavity formed after elevation of the collapsed posterior facet was filled by cancellous graft in 40 patients. The fixation materials applied to the patients in this study were anatomic low-profile calcaneal plates with lockable headless screws.

After the first dressings, splint was removed and active motion was started with compressive bandage. Patients who had clinical and radiographic union at 6-8th weeks time and who had no problem of wound site were allowed to walk with full load.

Statistical Analysis

Frequency analysis was used as a descriptive statistical method. Statistically, only mean values were given in this study. Statistical analyzes were performed with using SPSS 19.0.

RESULTS

The mean follow-up period was 25.8 months (8-56 months). After discharge, the patients were called for routine follow-up visits every 15 days, then monthly checks in the first 1.5 months, then every 3 months after the 6th month and yearly after the 1st year. Patients with wound or nonunion problems were called to the controls more frequently. In addition to physical and radiological examinations, American Orthopaedic Foot and Ankle Society (AOFAS) posterior foot score, pain and clinical evaluations were performed.

The radiographs, tomography and postoperative radiographs of the patients were compared. Postoperative reduction success was evaluated quantitatively by evaluating Böhler and Gissane angles on lateral radiographs.

The mean AOFAS score was 83.9. Distributions of AOFAS scores according to the fracture type were seen in Table 1; this was 94.6 in patients with tongue fractures, 88 in Sanders type 2 patients, 82.8 in Sanders type 3 patients and 78.3 in Sanders type 4 patients. Postoperative Gissane angles of the patients were 123 in tongue type, 125.9 in Sanders type 2, 123.3 in Sanders type 3, and 115.1 in Sanders type 4; Böhler angles were found to be normal as; 34 in tongue type, 29.2 in Sanders type 2, 27.6 in Sanders type 3, and 26.5 in Sanders type 4. The mean

Table 1. AOFAS hindfoot scores according to fracture type	
	AOFAS scores
Tongue type	94.6
Type 2	88
Type 3	82.8
Type 4	78.3
AOFAS: American Orthopaedic Foot and Ankle Society	

preoperative and postoperative Gissane and Böhler angles of the patients were shown in Table 2.

Complications (24.4%) developed in 11 patients. In Table 3 distribution of complications could be seen. In 5 of these patients (11.1%) wound site necrosis or opening was seen. Two of these 5 patients were treated with appropriate antibiotherapy and the other 2 patients (4.4%) required implant removal. One of the patients whose implants were removed had insulin dependent diabetes and the other had epilepsy. Removal time after surgery was 8 months in diabetic patient and 12 months in epileptic patient. In 1 patient, debridement and primary closure was performed in the 6th postoperative month because the necrosis area did not close. 1 patient developed pseudoarthrosis due to deep infection. Subtalar arthrodesis was performed and implants were removed. One patient required implant removal due to lateral compression of the implant. A patient with type 3 BC fracture did not relieve the pain and underwent subtalar arthrodesis. During follow-up, the patient had no complaints. Sudeck atrophy was observed in 3 patients at 3 months postoperatively. Physical therapy and calcium phosphate-vitamin D treatment were started. After 3 months of treatment, complaints disappeared.

DISCUSSION

Increasing technological developments all over the world; the incidence of calcaneal fractures increases with the increase in occupational accidents and high speed automobile use.

It is more common in the male population as it is mostly seen after heavy work accidents. Some studies have shown that patients with calcaneal fractures are mostly seen in men aged 40 years (2-4). In our study, it was determined that 80%

of the patients were male and the mean age was 39.9 years in accordance with the literature.

Although the time to return to work with non-surgical treatment appears to be shorter, patients have been reported to have worse long-term outcomes (5). In our study, we found that the mean time to return to work was 5.5 (between 4-11 months) months in our patient group who underwent surgery.

Although treatment uncertainties remain for physicians at present, many orthopedists now use the Sanders classification system based on CT, which is easily accessible and closely related to patient prognosis. According to this classification, non-displaced intraarticular fractures (Sanders type 1) are treated conservatively. In Sanders type 2 and 3 fractures, if there are no contraindications, open reduction and internal fixation are recommended. There are different opinions in type 4 fractures. Primary arthrodesis, open reduction and internal fixation, conservative treatment and subsequent subtalar arthrodesis are the treatment modalities (1,5-9). Preoperative CT images were obtained in all patients included in this study and the patients were classified according to the Sanders classification system (1).

Sanders et al. (7) reported that anatomic reduction was necessary to achieve good and excellent results in a series of 120 patients with 29-month follow-up, but that anatomic reduction may not be accurate due to cartilage damage at the time of trauma. In addition, they stated that the surgeon who would perform calcaneal fracture surgery had a learning curve of 35-50 cases. They found good and excellent results in 73% of patients with type 2 fractures and 70% in patients with type 3 fractures. In this study, they emphasized that primary arthrodesis is necessary in type 4 fractures. When the surgery is decided, it is very important to decide which approach provides the most ideal vision. In the mid-1970s, when surgery became popular again in the treatment of calcaneal fractures, many invasive techniques such as medial, sustentacular, sinus tarsi, as well as lateral extensive approaches have been described (10-14). Minimally invasive techniques are impressive because they cause less damage to the soft tissue. However, reduction of joint compliance is considered indirect. Burdeaux (15), Stephenson (16), Essex Lopresti (17), Rammelt et al. (18) and Gavlik et al. (19) treated calcaneal fractures using a variety of minimally invasive techniques and recommended minimally invasive methods.

Today, many researchers have agreed on the extensile lateral approach, which is a no-touch technique for intraarticular displaced calcaneal fractures (7,10,11,13,14,20,21). This approach, known as the Kocher incision, was popularized by Palmer (22) in the 1940s. However, they could not obtain satisfactory results due to high infection rate and wound

Table 2. Comparison of Gissane and Böhler angles according to fracture type

	Pre-operative		Post-operative	
	Gissane	Böhler	Gissane	Böhler
Tongue type	121	-43	123	34
Type 2	126.4	2.6	125.9	29.2
Type 3	132.2	7.2	123.3	27.6
Type 4	124.1	3.5	115.1	26.5

Table 3. Complications after surgery

Complication	Number of patients	%
Wound site necrosis	5	11.1
Sudeck atrophy	3	6.6
Deep infection	1	2.2
Compression of the implant	1	2.2
Subtalar arthrodesis	1	2.2

problems. Letornel modified the Palmer approach by removing the incision margins more posteriorly and inferiorly as a full-thickness skin flap. Thus, it caused less peroneal tendon damage, sural nerve lesion, calcaneofibular ligament damage and skin problem. This approach has been used in many large-scale studies (7,10,11,13,20,23-26). In our study, we used extended lateral approach in 41 of 45 patients. We operated one patient in type 3 AB class and three patients with tongue fractures with minimally invasive and percutaneous screwing.

However, when surgery is decided, its timing is crucial because massive edema makes surgery contraindicated (27,28). Rammelt and Zwipp (6) proposed the wrinkle test for surgical timing. The general opinion of calcaneal fractures is that conservative treatment should be considered because of joint consolidation when the waiting period exceeds 3 weeks (6,7,25,29). In our practice, we are in favor of postponing surgery until the patients' fracture test is positive. In our study, we found that the time from the operation to the postoperative period of our patients was 14.3 days (1,30).

The general opinion for the postoperative period is to start early movement. Zwipp et al. (11) (6,10,18) recommended movement to patients on the first postoperative day, while many authors recommended waiting for sutures until removal. There are also differences of opinion on the issue of weight bearing. Some authors suggested partial load on the patient's own shoes as soon as possible (11,30), whereas Sanders recommended that the foot be kept in a neutral position to avoid crop contracture and that a weight bearing would be given after 12 weeks. In our study, we started compressing the bandage on the post-op day 2 when the patients were draining. All patients were given weight at 6th and 8th weeks.

Complications are a common problem in the treatment of calcaneal fractures. Superficial skin necrosis is the most common complication of operative treatment (6,7,27,31,32). It can be seen in an average of 14% of cases after the standard extended lateral approach. (2,6,13,32,33) In our study, complications occurred in 11 patients (24.4%) after calcaneus surgery. Five of these patients (11.1%) were wound necrosis or opening. Two of these 5 patients were treated with appropriate antibiotherapy and the other 2 patients (4.4%) required implant removal. One of the patients whose implants were removed had insulin dependent diabetes and the other had epilepsy. In 1 patient, debridement and primary closure was performed in the 6th postoperative month because the necrosis area did not close.

Due to the popularity of the extended lateral approach, the most common cutaneous sural nerve lesion was not seen in any of our patients (7,34,35). Sudeck atrophy was observed in 3 patients at 3 months postoperatively. Physical therapy and calcium phosphate-vitamin D treatment were started. After 3 months of

treatment, complaints disappeared. Deep vein thrombosis was not seen in any patient.

Various scales are used in the clinical evaluation of patients after calcaneus fracture. Similar scales with similar features are Maryland foot ratings, Creighton-Nabraska foot ratings, and AOFAS hind foot scale (36). In his study of 120 patients, Sanders (8) used the Maryland foot score and stated that anatomic reduction is essential to achieve good results, but that cartilage damage during trauma cannot be guaranteed. In our study consisting of 45 patients, AOFAS hindfoot evaluation scale was implemented. Accordingly, we achieved excellent results in 23.5%, good results in 50%, moderate results in 14.7% and poor results in 11.7%. In our study, we think that even in fractures in which we achieved anatomic reduction in type 3 and type 4 fractures, cartilage destruction and the large number of fracture fragments in the posterior facet was the reason for low results. In line with this idea, we found that the Sanders classification gives information about the prognosis in direct proportion with the thesis.

CONCLUSION

Calcaneal fractures constitute 2% of all fractures and 60% of tarsal bone fractures. It can cause socioeconomic problems both for the patient and the public in patients who cannot be treated appropriately because it occurs in active individuals around the age of 40 years. Nowadays, the general treatment principle of displaced intra-articular calcaneal fractures is anatomic reduction and early onset of motion due to the development of both diagnostic and treatment alternatives. The surgeon's experience in the treatment of calcaneal fractures, factors such as chronic diseases of the patient and the damage of the cartilage at the time of injury may affect the success of the treatment. In addition, the increase in the population in accordance with the Sanders classification adversely affects the prognosis. Therefore, the patient should be informed that a successful surgery cannot always have successful results.

Ethics

Ethics Committee Approval: Okmeydanı Training and Reserach Hospital Ethic Committee approved the study (28.04.2015/318).

Informed Consent: All participants give informed consent for the participation in this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Characteristics of Spontaneous Supratentorial Intracerebral Hematomas: A Retrospective Analysis of 108 Consecutive Patients

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Abstract

Objective: Spontaneous supratentorial intracerebral hematomas (SSIH) are among the pathologies that cause serious mortality and morbidity. The objective of this study was to assess the demographic and clinical characteristics, treatment approaches and outcomes of SSIH patients.

Methods: We retrospectively analyzed 108 patients who were diagnosed with SSIH between December 2017 and December 2018.

Results: Eighty nine (82.4%) of 108 patients were treated conservatively and 19 (17.6%) patients were treated surgically. Fifty seven (52.8%) of the patients were male and 51 (47.2%) were female. The mean age was 64.5 ± 14.0 . The mean Glasgow Coma scale (GCS) of the patients was 12.3 ± 3.0 , and the GCS of the surgical group was significantly lower than the conservative group ($p < 0.05$). The mean hematoma volume was 40.1 ± 51.6 mL, and the hematoma volume in the surgical group was significantly higher than the conservative group ($p < 0.05$). Intraventricular hemorrhage and midline shift positivity were significantly higher in the surgical group ($p < 0.05$). The mean Intracerebral Hematoma score (IHS) of the patients was 1.3 ± 1.4 . IHS was significantly higher in the surgical group ($p < 0.05$). Mortality rates in the first month, sixth month and first year were significantly higher in the surgical group ($p < 0.05$).

Conclusion: Because of the high mortality rate and severe morbidities that occurs after the SSIH, it is mandatory to identify and apply standardized treatment strategies for patients.

Keywords: Stroke, spontaneous intracerebral hematoma, intracerebral hematoma score, treatment

INTRODUCTION

Intracerebral hemorrhages constitute 6.5%-19.9% of all stroke causes (1). Spontaneous supratentorial intracerebral hematomas (SSIH) are among the pathologies that cause serious mortality and morbidity; however, there is still no consensus regarding their treatment (2). To date, several studies have compared conservative and surgical treatments, including current treatment approaches (3-5). Based on the literature review, conventional surgical treatment can be considered to have better results for superficial and small SSIHs than conservative treatments, and minimally invasive surgical methods have more favorable results in deep-seated SSIHs. Therefore, in this

study, we aimed to investigate the demographic and clinical characteristics, treatment approaches, and outcomes of patients with SSIH treated in our clinic.

METHODS

Patients with intracerebral hematoma admitted to our emergency department between December 2017 and December 2018 were retrospectively reviewed. A total of 108 patients diagnosed with SSIH using computed tomography (CT) scans were included in this study. Patients with trauma, aneurysm, vascular malformation, and hematomas due to tumor pathology and similar etiologies were excluded. In addition, patients with posterior fossa



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hematomas were also excluded from this study due to differences in clinical features and treatment approach. Medical history (in some cases, of patients' relatives) and demographic information were obtained, and detailed neurological examinations were performed. The neurological status of the patients was evaluated using the Glasgow Coma scale (GCS) in the emergency department, and the first prognostic evaluation was performed (6). Arterial blood pressure measurements and biochemical tests were performed to exclude possible differential diagnoses. Metabolic parameters (glucose, electrolytes, and creatinine) and hematologic parameters (complete blood count, prothrombin time, international normalized ratio, and partial thromboplastin time) were analyzed through blood examinations. The hematoma volume, hemispheric side (right or left), location (deep or lobar), lobe (frontal, temporal, parietal, insular, occipital), and intraventricular hemorrhage were determined using CT. Hematoma volume was calculated according to the ABC/2 rule (7). A midline shift of >5 mm was considered positive. The Intracerebral Hematoma score (IHS) was calculated and recorded (8). After these stages, the treatment plan was firstly determined. As surgical intervention, patients underwent hematoma evacuation by craniotomy or decompressive craniectomy or external ventricular drainage (EVD) for intraventricular hemorrhage. Conservatively treated patients were monitored during the post-hospitalization follow-up. The multimodal treatment for these patients was planned in collaboration with the anesthesiology and neurology departments. Mortality rates were calculated by comparing two different treatment methods. This retrospective study was performed in accordance with the ethical standards provided by the Helsinki Declaration. Informed consent form was obtained from all patients.

Statistical Analysis

The results for continuous variables are provided as mean \pm standard deviation (SD). The Kolmogorov-Smirnov test was used to evaluate the distribution normality of continuous variables. Student's t-test or Mann-Whitney U test was used to compare independent continuous variables between the two groups depending on whether the statistical hypotheses were fulfilled. A p value of <0.05 was considered statistically significant. SPSS 22.0 program (IBM Software, New York, USA) was used for analysis.

RESULTS

The demographic, clinical, radiological, and prognostic characteristics of 108 patients [57 (52.8%) men and 51 (47.2%) women] are shown in Table 1. Among them, 89 (82.4%) patients were treated conservatively and 19 (17.6%) were treated

surgically. As the mean age was 64.5 ± 14.0 (mean value \pm SD) years, the age and sex distribution of treatment groups was not statistically significant ($p > 0.05$). The mean GCS was 12.3 ± 3.0 , which was significantly lower in the surgical group than in the conservative group ($p < 0.05$).

About 84.2% of patients had arterial hypertension on admission. However, no significant difference was observed between the treatment groups with respect to comorbidities ($p > 0.05$). The mean hematoma volume was 40.1 ± 51.6 mL, which was significantly higher in the surgical group than in the conservative group ($p < 0.05$). Intraventricular hemorrhage and midline shift positivity were significantly higher in the surgical group ($p < 0.05$). However, the difference in the hemisphere side (right/left) and location (deep/lobar) of the hematoma was not significant between the treatment groups ($p > 0.05$). The patients' mean IHS was 1.3 ± 1.4 . Table 2 shows IHS according to the treatment groups. The IHS score was significantly higher in the surgical group than in the conservative group ($p < 0.05$). Table 3 shows the mortality rates, which were significantly higher in the surgical group during the first month, sixth month, and first year than those in the conservative group ($p < 0.05$).

DISCUSSION

SSIH, also known as primary intracerebral hematomas, constitute 78%-88% of intracerebral hemorrhages (9,10). In regard to their pathogenesis, they were considered to occur with spontaneous rupture due to small arterial or arteriole wall damage caused by hypertension or amyloid angiopathy (10,11).

The incidence of intracerebral hematoma in elderly patients (>65 years) was higher than that in other age groups (12,13). However, whether sex is a risk factor or not remains controversial (13-15). Different results have been claimed to be obtained from different populations or countries. In this study, 57 (52.7%) patients were older than 65 years, with a mean age of 64.5 years. Furthermore, no significant difference in age and sex was observed between the treatment groups.

The most common risk factor for SSIHs is hypertension, which is responsible for the etiology in approximately 60%-70% of patients (16,17). Qureshi et al. (10) reported that intracerebral hematomas occurring due to hypertension are frequently located in the basal ganglia. Sacco et al. (13) reported in their case series of 549 patients that 75.6% had hypertension and similar rates of SSIH localization (deep or lobar) were also determined. In this study, hypertension was observed in 84.2% of patients. However, patients with lobar hematoma were found to be more hypertensive with a slight difference (55.6%).

In the literature, various studies on the SSIH treatment that proposed different treatment features have been conducted. The World Health Organization treatment guidelines, prepared almost 30 years ago, only recommended surgical treatment for large-volume SSIHs (18), whereas at the same time studies have also suggested the surgery-only treatment approach for small subcortical SSIHs (3). Multiple attempts have been made to eliminate this uncertainty, and large multicenter randomized

clinical trials have already been conducted. The first and best known is the STICH study, published in 2005 (19). According to the results of this study, early surgery is not more effective than conservative treatment. However, when subgroups such as superficial (lobar) intracerebral hematomas (not the focus of this study) were examined, early surgery was found to provide better results than conservative treatment. In the following years, the STICH 2 study was conducted as a continuation study

		Total	Conservative group	Surgery group	p value
Demographic features					
Age	(M ± SD)	64.5±14.0	64.7±13.7	63.5±15.8	>0.05 ^t
Sex					
Male	(n, %)	57, 52.8%	47, 52.8%	10, 52.6%	>0.05 ^{x2}
Female	(n, %)	51, 47.2%	42, 47.2%	9, 47.4%	
Clinical features					
Initial GCS	(M ± SD)	12.3±3.0	13.0±2.4	9.2±3.5	<0.05 ^m
3-8	(n, %)	14, 13.0%	5, 5.6%	9, 47.4%	<0.05 ^{x2}
9-12	(n, %)	25, 23.1%	20, 22.5%	5, 26.3%	
13-15	(n, %)	69, 63.9%	64, 71.9%	5, 26.3%	
Comorbidities					
HT +	(n, %)	91, 84.2%	75, 69.4%	16, 84.2%	>0.05 ^{x2}
DM +	(n, %)	22, 20.3%	18, 16.6%	4, 21.0%	>0.05 ^{x2}
AC +a	(n, %)	49, 45.3%	37, 34.2%	9, 47.3%	>0.05 ^{x2}
Radiological features					
Hematoma volume (mL)	(M ± SD)	40.1±51.6	27.5±38.3	99.5±64.5	<0.05 ^m
IVH					
-	(n, %)	78, 72.2%	76, 85.4%	2, 10.5%	<0.05 ^{x2}
+	(n, %)	30, 27.8%	13, 14.6%	17, 89.5%	
Midline shift					
-	(n, %)	81, 75.0%	75, 84.3%	6, 31.6%	<0.05 ^{x2}
+	(n, %)	27, 25.0%	14, 15.7%	13, 68.4%	
Hemispheric side					
Right	(n, %)	52, 48.1%	40, 44.9%	12, 63.2%	>0.05 ^{x2}
Left	(n, %)	55, 50.9%	48, 53.9%	7, 36.8%	>0.05 ^{x2}
Bilateral	(n, %)	1, 0.9%	1, 1.1%	0, 0.0%	>0.05 ^{x2}
Location					
Lobar ^b	(n, %)	60, 55.6%	47, 52.8%	13, 68.4%	>0.05 ^{x2}
Deep	(n, %)	48, 44.4%	42, 47.2%	6, 31.6%	>0.05 ^{x2}
Prognosis					
IHS	(M ± SD)	1.3 ± 1.4	0.9±1.2	2.8±1.1	<0.05 ^m
Follow-up (day)	(M ± SD)	358.9±265.6	410.9±250.5	268.6±308.3	>0.05 ^m

^aIncludes all anticoagulant-antiaggregant treatments used during hospital admission, ^bStatistical analysis was performed for each lobe separately, but since there was no significant difference, the results were reported under a 2 single heading, ^tt- test, ^{x2}Chi-square test, ^mMann-Whitney U test, M: Mean, SD: Standard deviation, n: Number of patients, GCS: Glasgow Coma score, HT: Hypertension, DM: Diabetes mellitus, AC: Anticoagulant, mL: Milliliter, IVH: Intraventricular hemorrhage, IHS: Intracerebral Hematoma score

with a focus on this subject, and the results were published (4). In support of subgroup results in the first STICH study, early surgery has been found to have a clinically significant advantage over conservative treatment, especially in lobar hematomas without intraventricular hemorrhage. In the literature, studies have also investigated the appropriate surgical treatment methods for deeply located and/or with ventricular opening intracerebral hematomas. Several recent studies have been performed, and some of them were successfully conducted, especially with minimally invasive surgery (endoscopic surgery), hematoma drainage, or clot removing techniques (5,20-23). However, most of these specialized technical equipment and medications are not available for all treatment centers, and because intracerebral hematomas are considered as emergency neurosurgical pathology, deciding the timing of surgery and choosing the appropriate treatment option are extremely important. Although surgical indications for intracerebral hematomas were not standardized, our approach was to evacuate the hematoma in patients with high-volume lobar hematomas with low-onset GCS and midline shift (risk of brain herniation). Decompressive craniectomy was performed in a deeply located hematoma in the worse clinical situation. EVD was performed to prevent complications such as acute hydrocephalus.

IHS is a scoring system used to gain insight on the prognosis of patients with intracerebral hematoma but does not have an effect on surgical decision (8). The focus of this study is

not on developing a new scoring system. However, as seen in the literature, there is no standardized clinical prognostic classification (24-26). Upon the evaluation of the results in this study, the mean IHS was found to be 1.3 ± 1.4 . IHS in the surgical group was higher than that in the conservative group. Although the midline shift is one of the most helpful findings for the surgeon to plan the surgical treatment of these pathologies, it is not used in calculating IHS. We consider that this finding may also be an important criterion for the life expectancy and prognosis of patients with SSIH after 1 month and that such modification can be made.

The 1-year mortality of patients was high (42.5%), as shown in Table 3. However, this is believed to be not due to the primary effect of the hematoma but rather due to comorbidities. Alsumrain et al. (27) reported that patients with SSIH more frequently have pneumonia. In addition, although not the focus of this study, the most important feature of SSIHs is the presence of comorbidities, such as hemiparesis, hemiplegia, and spasticity, even in patients with good prognosis. Patients with neurological dysfunction are more likely to die due to other causes.

This study has some limitations. First, intracerebral hematomas were evaluated as one of the emergency neurosurgical pathologies with controversial surgical treatment based on our own perspective. Second, this was a single-centered study, and therefore, the incidence-prevalence of the disease was not determined. Finally, although this was a retrospective study, all patients with intracerebral hematoma admitted to our emergency department underwent the standardized diagnostic, radiological, and clinical examination.

CONCLUSION

SSIH is a pathology with a high mortality rate and causes various neurological disorders and severe comorbidities even in non-life-threatening conditions, which worsens the quality of life. The standardization of current diagnosis and treatment algorithms can significantly improve the survival and quality of life of these patients.

Ethics

Ethics Committee Approval: This retrospective study was performed in accordance with the ethical standards provided by the Helsinki Declaration.

Informed Consent: Informed consent form was obtained from all patients.

Peer-review: Externally peer-reviewed.

IHS	Conservative group	Surgery group	Total
0	47	0	47
1	17	2	19
2	11	5	16
3	11	8	19
4	3	2	5
5	0	2	2

IHS: Intracerebral Hematoma score

	Conservative group	Surgery group	Total	p value
Mortality (1. month)	15.3%	52.6%	22.2%	<0.05 ^{x2}
Mortality (6. months)	24.7%	57.8%	30.5%	<0.05 ^{x2}
Mortality (12. months)	26.9%	63.1%	42.5%	<0.05 ^{x2}

^{x2}Chi-square test

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Elevated Neutrophil-to-Lymphocyte Ratio May Be Associated with Overactive Bladder Patients

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Abstract

Objective: Overactive bladder (OAB) may be interrelated with chronic inflammation. The aim of this study was to assess the role of neutrophil-lymphocyte ratio (NLR) levels in men and women with OAB symptoms.

Methods: Between January 2017 and February 2018, a total of 157 subjects (77 OAB patients and 80 controls) were included in the study. The subjects divided into two groups. Group 1=OAB patients and group 2=normal controls. Patients with active urinary tract infections, previous pelvic surgery or neurogenic patients were excluded. The enrolled both patients and control group were questioned using the 8-item OAB questionnaire (OAB-v8) complete blood count and serum C-reactive protein (CRP) levels were measured in the first visit.

Results: The mean NLR was 1.73 ± 0.67 in patients and 1.48 ± 0.75 in control groups ($p < 0.001$). The NLR and CRP levels were both statistically significant higher in OAB patient group ($p = 0.03$ for CRP and $p = 0.001$ for NLR). There was positive correlation between OAB-v8 scores and NLR ($p < 0.001$, $r = 0.215$)

Conclusion: High serum NLR levels were observed in OAB patients. Our results support the association between chronic inflammations of the bladder in OAB patients.

Keywords: Overactive bladder, neutrophil-to-lymphocyte ratio, urgency, inflammation

INTRODUCTION

Overactive bladder (OAB) is a multifactorial and widespread health disorder, identified by the International Continence Society as an Urgent Characterizing syndrome, with or without urinary incontinence, often accompanied by frequency and nocturia when there is no urinary tract infection or any other kind of apparent pathology (1). OAB is a common situation in both sexes and has a noteworthy effect on quality of life and economic burden (2-4). OAB is a highly extensive condition affecting 12-17% of men and women. Approximately 28% of men and 49% of women reporting symptoms of OAB women report urinary incontinence (UI) with urgent UI (4).

Epidemiological studies have suggested that inflammation may play a role in the growth and progress of lower urinary tract symptoms (LUTS). Rohrmann et al. (5) found that men with detectable C-reactive protein (CRP) levels had a higher likelihood of LUTS than men with undetectable CRP levels. Clinical investigations of bladder biopsy findings in patients with OAB show that inflammation is associated with OAB pathophysiology (6). A recent study also demonstrated that higher levels of urinary inflammatory biomarkers are identified in patients with OAB (7). While the molecular mechanisms underlying the etiology and pathophysiology of OAB are still largely unknown, the interaction between the urinary system and the immune system has been shown to have a notable part in the pathophysiology of OAB



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(8). Detrusor overactivity has often been regarded as the primary cause of OAB. However, the potential role of inflammatory processes in the pathophysiology of OAB and development of OAB has not been well assessed. While the monitoring of cytokines in blood plasma may improve our understanding of the process that leads to OAB the technical difficulties and costs related with the use of these inflammatory markers such as interleukins, tumor necrosis factor-alpha, interferon gamma, and CRP, in routine clinical practice may limit their use.

Alternatively, the neutrophil-lymphocyte ratio (NLR) can be rapidly and inexpensively attained from a differential white blood cell (WBC) count. It is a marker of inflammation and predicts the prognosis of disease. The NLR has already been shown to play a role in inflammatory diseases (9-11), but its relationship with OAB continues to be vague. Thus, the aim of the study we conducted was to evaluate the association between OAB and inflammation, as measured by the NLR, among men and women with OAB.

METHODS

Cross-sectional data was collected female patients with OAB based on the symptoms of urgency with/without urgency incontinence who visited outpatient urological clinics for treatment from January 2017 to February 2018. The study was confirmed by the Institutional Review Board of Okmeydanı Training and Research Hospital (2017/380) and written consent was acquired from all participants. The study was carried out in accordance with the principles of the Helsinki Declaration. Power analysis to estimate the sample size was based on the CRP values in a similar previous study (12). Assuming a power of 0.80 and α value of 0.05, a sample size of 75 patients was found to be sufficient for each group.

Baseline characteristics were collected from each patient's medical records and included data on age, body mass index (BMI), smoking, previous diseases, history of bladder or urethral surgery, medication, and comorbidities. All patients had urinary ultrasonography and urine examination; urine culture, serum creatinine, and complete blood count were examined for the differential diagnosis. Patients with previous bladder or urethral surgery, active urinary tract infections, medication use for OAB, diabetes or possible neurogenic lesions, cardiovascular diseases, malignancy were excluded from the study. The control group included individuals with no active urologic disease or LUTS. Uroflowmetry and postvoid residual urine volume were measured at the first visit to rule out bladder outlet obstruction. The enrolled both patients and control group were also

questioned using the 8-item OAB questionnaire (OAB-v8) (13). Also, a 3-day voiding diary was kept, which was used to verify urgency, urgency urinary incontinence, and functional bladder capacity.

The complete blood count was obtained by a hematology analyzer (Coulter Gen-S Hematology Analyzer; Beckman Coulter Corp, Hialeah, FL, USA). The total WBC was recorded, along with the neutrophil and lymphocyte counts. The NLR was calculated by dividing the neutrophil count by the lymphocyte count and platelet count by the lymphocyte count, respectively.

Statistical Analysis

SPSS 22.0 program (SPSS, Chicago, IL, USA) was used in the analyzes. The distribution of variables was determined by means of using the Kolmogorov-Smirnov test. Independent samples t-test and Mann-Whitney U test were used for the analysis of quantitative independent data. Pearson chi-square test was used in the analysis of qualitative data. Pearson correlation analysis was used in the correlation analysis. The NLR cut-off value was determined according to the level of specificity and sensitivity obtained from the area under the receiver operator characteristics (ROC) curve for patients with and without OAB. A p value of <0.05 was considered to be statistically significant.

RESULTS

A total of 77 patients and 80 control subjects were inscribed. The demographic data are listed in Table 1. Age, BMI, smoking and alcohol consumption status were not significantly different between the groups ($p>0.05$).

The mean NLR was 1.73 ± 0.67 in patients and 1.48 ± 0.75 in control groups ($p=0.001$). The mean neutrophil, lymphocyte, platelet, NLR and CRP levels were given in Table 2. The NLR and CRP levels were both statistically significant higher in OAB patient group ($p=0.03$ for CRP and $p=0.001$ for NLR). There was positive correlation between OAB v8 scores and NLR ($p<0.001$, $r=0.215$) (Figure 1).

	OAB Patients (n=77)	Control (n=80)	p
Age (mean, SD)	45.15±16.54	43.31±15.39	0.47 ^t
BMI (mean, SD)	27.05±5.17	27.45±4.38	0.59 ^t
Smoking status (n/%)	15/19.4	14/17.5	0.193 ^c
OAB v8 score (mean, SD)	18.57±2.84	0.35±1.01	<0.001 ^u

^tIndependent t-test, ^cChi-square test, ^uMann-Whitney U test, SD: Standard deviation, OAB v8: 8-item overactive bladder questionnaire

The ROC area of serum NLR levels to predict OAB was 0.66 (p=0.013, 95% confidence interval 0.57-0.75). The NLR cut-off point of 1.39 (sensitivity 65.4%, specificity 61%, positive predictive value 59.1%, negative predictive value 62.4%) (Figure 2).

DISCUSSION

This is the first study to investigate the relationship between OAB and inflammatory markers NLR. Results of this cross-sectional study demonstrate a significant relationship between the elevated NLR and OAB symptoms in patients. These results assist to hypothesis that inflammation is effective in the development of OAB. The findings from our study show that

this inflammatory marker is suitable for screening to identify patients with OAB.

Prior studies have shown that systemic inflammatory processes are allied with OAB. It has shown that OAB may result from sterile trauma or stress, or both, and is based on evidence of bladder excessive urinary inflammation cytokines and chemokines, and is related to bladder inflammation involving an interaction involving bladder overactive parasympathetic and peptidergic/sensory disturbances (7). A bladder biopsy study in patients with OAB also suggests that bladder inflammation is associated with OAB pathophysiology (6). Another study revealed that intravesical instillation of cyclooxygenase-2 inhibitor reduced detrusor hyperactivity and decreased the expression of inflammatory modulators in rat model (14). Additionally, Kupelian et al. (15) showed increased risk of OAB with higher CRP levels, which is an inflammatory marker, in both men and women in their study. Baseline data from the Reduction by Dutasteride of Prostate Cancer Events trial demonstrate a relatively weak but significant correlation between the degree of inflammation and LUTS assessed by the International Prostate Symptom score (IPSS). Chronic inflammation was related with both storage and voiding sub scores of the IPSS (16). Studies have suggested that the likeness of clinical trials with advanced inflammatory markers in male and female genders might show a familiar pathophysiology responsible for OAB.

Table 2. Comparison of OAB patient and control groups

	OAB Patients (n=77)	Control (n=80)	p
Hemoglobin (g/dL) [Med (Q1-Q3)]	14.70 (13-15)	13.35 (12.60-14)	0.151 ^u
Neutrophil (10 ³ /μL) [Med (Q1-Q3)]	3.89 (2.7-4.5)	3.5 (2.6-4.3)	0.03 ^u
Lymphocyte (10 ³ /μL)	2.58±0.71	2.51±0.63	0.458 ^t
Monocyte (10 ³ /μL)	0.54±0.19	0.59±0.12	0.064 ^t
Basophil (10 ³ /μL)	0.18±0.12	0.25±0.16	0.188 ^t
Eosinophil (10 ³ /μL)	0.03±0.03	0.03±0.02	0.381 ^t
Platelet (10 ³ /μL)	100.82±38.04	101.89±45.06	0.402 ^t
CRP (mg/L)	4.87±5.86	3.03±1.96	0.372 ^t
NLR	1.73±0.67	1.48±0.75	0.001 ^t

OAB: Overactive bladder, NLR: Neutrophil-to-lymphocyte ratio, ^tIndependent t-test, ^uMann-Whitney U test

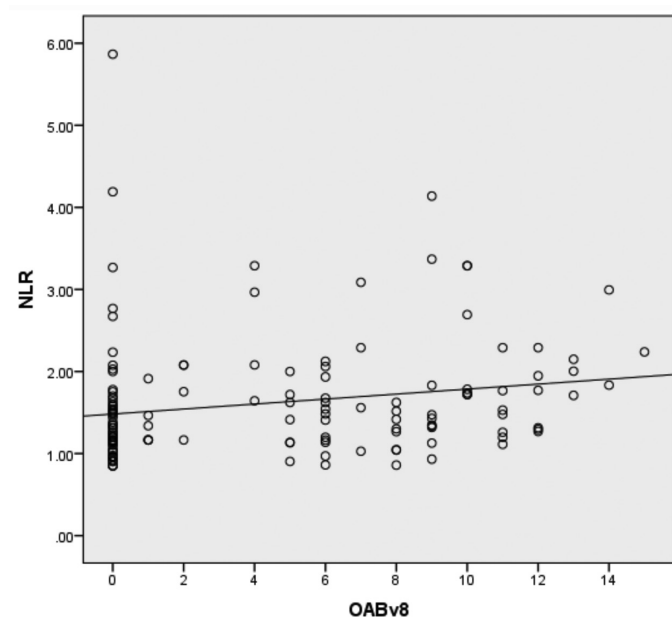


Figure 1. The Association of Serum NLR with OAB scores
OAB: Overactive bladder, NLR: Neutrophil-to-lymphocyte ratio

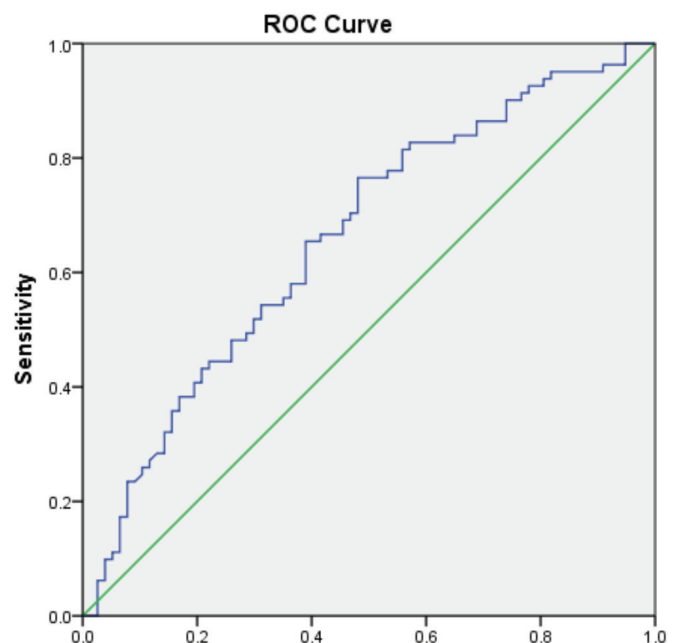


Figure 2. The ROC curve of NLR. Cut-off point 1.39 [area under curve: 0.66 (0.57-0.75)] was considered significant for OAB
ROC: Receiver operator characteristics, NLR: Neutrophil-lymphocyte ratio, OAB: Overactive bladder

While these inflammatory markers may improve our understanding of OAB, the technical difficulties and costs associated with measuring them in routine clinical practice limit their use. Therefore, the goal of this study is to determine the relationships between OAB and NLR quickly and cheaply.

Neutrophils have several potent effector mechanisms to combat and eventually devastate tissues. Oxidative mechanisms that result in the production of reactive oxygen species, the release of several peptides, and the formation of neutrophil extracellular traps have detrimental effects on bladder (17). Since neutrophilia and lymphocytopenia occur after systemic inflammation (18), the increase in NLR found in those with chronic inflammation may also affect the patients with OAB.

Recently, studies have shown that chronic inflammation is associated with an increased neutrophil lymphocyte ratio. The NLR have been used to detect inflammation in cardiovascular diseases, prevalent chronic diseases, infectious diseases, various kinds of malignancies, and several other inflammatory diseases (19-22). However, NLR has not previously been used to determine the association between inflammation and OAB. In this study, we found significant differences in the associations of OAB and the NLR between the patients with OAB and control group.

Systemic inflammation may, therefore, be one cause of OAB through unknown mechanisms. This study demonstrated that severity of disease was affected by the inflammatory markers that we studied. There were, however, limitations to our study that are worth mentioning. These include the nature of cross-sectional, as well as having a relatively small sample size. Additionally, the lack of subsequent NLR levels after treatment limits its potential role as a follow-up biomarker. Further research on the associations of OAB with the NLR is required to verify the results of our study.

CONCLUSION

This study shows that the serum NLRs of the OAB patients is higher than normal controls. These consequences extra proof to the accrued proof backing up an inflammatory role in the growth and progress of OAB. Longer studies are needed to better define the effect of inflammation and to inform the development of the interventions of anti-inflammatory agents in OAB treatment.

Ethics

Ethics Committee Approval: The study was confirmed by the Institutional Review Board of Okmeydanı Training and Research Hospital (2017/380).

Informed Consent: Written consent was acquired from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.G.Ç., R.B.D., Design: M.G.Ç., S.Ö., Data Collection or Processing: R.B.D., M.B., S.A., Analysis or Interpretation: M.G.Ç., A.Ö., Literature Search: R.B.D., M.G.Ç., F.A., E.M., Writing: M.G.Ç.

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

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Prevalence and Risk Factors of Urinary Incontinence in Poorly Educated Female Population

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Abstract

Objective: There is a significant inverse correlation between poor education level and one's awareness of his/her health status. Poorly educated patients presume most of the disorders as an expected progress of aging and daily life. In our study we aimed to clarify the prevalence of urinary incontinence (UI) in women with a poor educational level.

Methods: Female patients admitted to urology and gynecology outpatient clinics without UI complaints were enrolled into the study. Patients, who were uneducated or only literate, were defined as poorly educated. All patients were made to fill in Urinary Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) forms. Patients younger than 18 years, with a history of incontinence surgery and pelvic surgery, history of pelvic radiation, presence of urologic and gynecological malignancy or severe neurological diseases were excluded from the study.

Results: In study population, 236 patients (46.1%) had a complaint of UI. Patients with UI were at a significantly older age and they had higher Body Mass Index (BMI). UDI-6 and IIQ-7 scores were significantly higher in patients with UI. The BMI, history of difficult labor and presence of pelvic organ prolapse were significantly higher in patients with stress UI (SUI). Age, BMI, presence of diabetes mellitus, number of deliveries, history of difficult labor and presence of pelvic prolapse were significantly higher in patients with urgency UI.

Conclusion: Our study revealed that even not applying to hospitals with that complaints the incidence of UI was very high in poorly educated female population and higher BMI, presence of difficult labor, pelvic prolapse were risk factors for UI and SUI subtypes.

Keywords: Poorly educated, stress, urge incontinence

INTRODUCTION

Urinary incontinence (UI) is defined as the complaint of any involuntary leakage of urine and forms of UI are divided into three main subtypes as stress UI (SUI), urgency UI (UUI) and mixed UI (MUI), according to International Continence Society (1). Although, UI is not a life-threatening disorder, its adverse effects on quality of life, mental health and sexual behavior are well-known. Zaccardi et al. (2) stated that 12%-50% of middle-aged women were faced with UI. In another study, Hunskaar et al. (3) stated the wide range of UI prevalence in different countries such as Spain with 23% and France with almost 45%. Some

authors believed extensive differences between UI rates stem from ethnicity, age at which incontinence begins, heterogeneity of the population studied and educational level.

Previous reports demonstrated the significant inverse correlation between poor education level and one's awareness of his/her health status. Poorly educated patients presuming most of the disorders as an expected progress of aging do not benefit from patient information programs properly, causing inefficient and inadequate description of complaints. Pedro et al. (4) found that infertile people with low education level did not have adequate knowledge about their illness, interventions and campaigns.



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Similarly, Ramírez-Moreno et al. (5) stated low educated patients who were faced with stroke had a lower quality of health and life expectancy than high-educated patients. Also, Kubik et al. (6) investigated incontinence prevalence considering ethnicity and has come to the conclusion that low socioeconomic status decreases awareness of incontinence.

Although previous reports investigated the prevalence of UI in different ages, ethnicities, regions and socioeconomic status intensively, no study has yet to evaluate the impact of educational level. In present study, we primarily aim to clarify the prevalence of UI in women with a poor educational level.

METHODS

This study was performed after approval by Haseki Training and Research Hospital Ethics Committee (4532771-432). Form was obtained from the patients. Between February 2018 and August 2018, female patients admitted to urology and gynecology outpatient clinics without UI complaints in two hospitals, were enrolled into the study. Patients, who were uneducated or only literate, were defined as poorly educated and selected as candidates for the study. The charts of the patients were recorded prospectively in the electronic data system. Detailed medical history was obtained from each patient. Patients' age, Body Mass Index (BMI), presence of diabetes mellitus, menopause status, number of deliveries and abortuses were evaluated. Also, patients were made to fill in Urinary Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) forms. Exclusion criteria were being <18 years old, history of incontinence surgery and pelvic surgery, history of pelvic radiation, presence of urologic and gynecological malignancy. Also, patients with severe neurological diseases and patients who failed to fill in the form were excluded from the study.

Urinary Distress Inventory-6 Questionnaire

The UDI-6 questionnaire is a simple and lucid form to evaluate quality of life in patients with urinary incontinence. The UDI-6 evaluates the type and severity of urological symptoms with 6 questions and each question is scaled from zero to three according to the volume of the complaints. The questionnaire is divided into three subgroups of irritability symptoms, stress symptoms and obstruction symptoms/pain related to urination. Each question was designed with two questions. To obtain UDI-6 score for each patient, sum of scores was divided by six and then, multiplied by twenty-five (7).

Incontinence Impact Questionnaire-7

The IIQ form is developed by the Continence Program for Women Research Group with 30 questions to assess the effects of

UI in female patients' quality of life. Then, IIQ form was revised from 30 to 7 items for a more efficient and simplified use (IIQ-7). In IIQ-7 form, each question was scaled from 0 to 3.0 refers to "not at all"; 1 refers to "slightly"; 2 refers to "moderately"; and 3 means "greatly". To obtain IIQ-7 score, sum of the scores (range between 0-21) is divided by seven and then multiplied by 33.3 (100/3) and the scores are put on a scale from 0 to 100. If <2 response is missing, the average score of the questions is taken. If more than 2 items are missing, a total score cannot be calculated (8).

Statistical Analysis

The Statistical Package of Social Sciences for Windows (SPSS) version 20.0 was used for statistical analysis. The patients were categorized into groups according to presence of urinary incontinence, urge urinary incontinence, SUI and mixed incontinence. Categorical variables were presented as numbers and analyzed with chi-square test. Continuous variables were presented as mean \pm standard deviation and evaluated with independent sample t-test. Correlation analyses were done by Pearson's correlation coefficient. Logistic regression analyses, on the other hand, were used so as to find predictive factors for urinary incontinence. A statistical significance was noted when two tailed p value <0.05.

RESULTS

At the end of the study period, total of 512 patients were evaluated. The mean age and mean BMI were 49.3 years and 27.2 kg/m², respectively. Total of 72 patients (14.1%) had diabetes mellitus and 234 patients (45.7%) were in post-menopausal status. The mean number of deliveries was 3.1. Patients' demographic hallmarks were summarized in Table 1.

Table 1. Demographic characteristics of patients	
Number of patient	512
Age (year)*	49.3 \pm 13.5
BMI (kg/m ²)*	27.2 \pm 4.1
DM	72 (14.1%)
Menopause	234 (45.7%)
Number of deliveries*	3.1 \pm 2.1
Vaginal*	2.7 \pm 2.3
Cesarean*	0.4 \pm 0.8
Abortus number*	0.6 \pm 1.0
History of difficult labor	103 (20.1%)
Pelvic prolapsus	93 (18.2%)
*Mean \pm standard deviation, BMI: Body mass index, DM: Diabetes mellitus	

In study population, 236 patients (46.1%) (SUI in 51 patients, UUI in 102 patients and MUI in 83 patients) had a complaint of UI. Comparison of patients with and without UI has revealed that patients with UI were at a significantly older age and they had higher BMI and the higher rate of women were postmenopausal ($p=0.001$, $p=0.001$, $p=0.032$ respectively). Furthermore, the number of vaginal deliveries and abortus was higher ($p=0.011$ and $p=0.001$). Furthermore, they went through a difficult labor history, diabetes mellitus (DM) and pelvic organ prolapse ($p=0.005$, $p=0.006$ and $p=0.001$ respectively). Also, UDI-6 and IIQ-7 scores were significantly higher in patients with UI (28.6 vs 9.0, $p=0.001$ and 37.3 vs 13.3, $p=0.001$, respectively). The BMI (28.7 kg/m² vs 25.7 kg/m², $p=0.001$), presence of pelvic organ prolapse (31.4% vs 10.1%, $p=0.001$) were significantly higher in patients with SUI. In addition; age, BMI, presence of DM, history of difficult labor and presence of pelvic prolapse were significantly higher in patients with UUI ($p=0.001$ for each parameter). Also, the number of deliveries was significantly higher in patients with UUI ($p=0.027$). Moreover, patients with MUI were at a significantly older age and they had a higher BMI, DM and higher rate of postmenopausal status ($p=0.001$, $p=0.001$, $p=0.013$ and $p=0.012$ respectively). Additionally, abortus numbers and pelvic organ prolapse diagnosis were significantly higher in patients with MUI ($p=0.001$ and $p=0.02$). Also, UDI-6 and IIQ-7 scores were significantly higher in all UI subgroups ($p=0.001$ and $p=0.001$ for each subgroups) (Table 2).

Multivariable regression analysis revealed that higher BMI, history of difficult labor and pelvic prolapse were associated with UI ($p=0.01$, $p=0.02$ and $p=0.01$ respectively). Moreover, higher BMI and presence of pelvic organ prolapse increased the risk of SUI 3.78 and 3.9 times, respectively. Presence of DM, history of difficult labor and pelvic organ prolapse were found as the only risk factors for UUI in multivariable regression analysis ($p=0.01$ for each parameter). Lastly, higher BMI, abortion history and pelvic prolapse were the risk factors for MUI ($p=0.01$ for each parameter) (Table 3).

DISCUSSION

Education level plays an important role for one to discern the abnormal changes in his/her body and consult a physician. Many previous reports in different disciplines have demonstrated that poorly educated people do not seek medical support until disease begins to hinder daily physical activities, disease progression, or emergence of fatal complications. On the other hand, UI is not fatal disorder but its association with deteriorating the quality of life is well-known. As a result, diagnosing UI in poor educated

Table 2. Comparison of patients according to presence of UI and UI subtypes

	UI			SUI			UUI			MUI		
	Yes	No	p	Yes	No	p	Yes	No	p	Yes	No	p
Number of patient	236	276		51	276		102	276		83	276	
Age (year)*1	51.8±12.9	47.2±13.6	0.001	46.0±11.5	47.2±13.6	0.657	53.9±13.2	47.2±13.6	0.001	52.9±12.4	47.2±13.6	0.001
BMI (kg/m²)*2	29.0±3.7	25.7±3.9	0.001	28.7±4.3	25.7±3.9	0.001	28.4±3.3	25.7±3.9	0.001	29.9±13.5	25.7±3.9	0.001
DM³	44 (18.6%)	28 (10.0%)	0.006	3 (5.9%)	28 (10.0%)	0.340	24 (23.5%)	28 (10.0%)	0.001	17 (20.5%)	28 (10.0%)	0.013
Menopause³	121 (51.3%)	113 (40.9%)	0.032	18 (35.3%)	113 (40.9%)	0.604	54 (52.9%)	113 (40.9%)	0.087	49 (59.0%)	113 (40.9%)	0.012
Number of deliveries*1	3.4±2.3	2.9±2.0	0.005	3.4±2.2	2.9±2.0	0.066	3.6±2.5	2.9±2.0	0.027	3.3±2.0	2.9±2.0	0.068
Vaginal*2	3.0±2.4	2.5±2.2	0.011	3.2±2.3	2.5±2.2	0.036	3.1±2.6	2.5±2.2	0.107	2.9±2.2	2.5±2.2	0.089
Cesarean*2	0.4±0.8	0.4±0.9	0.496	0.2±0.7	0.4±0.9	0.048	0.5±0.9	0.4±0.9	0.165	0.4±0.7	0.4±0.9	0.240
Abortus number*1	0.8±1.1	0.5±1.0	0.001	0.6±0.9	0.5±1.0	0.124	0.5±1.0	0.5±1.0	0.330	1.1±1.3	0.5±1.0	0.001
History of difficult labor³	62 (26.3%)	41 (14.9%)	0.005	18 (35.3%)	41 (14.9%)	0.147	32 (31.4%)	41 (14.9%)	0.001	17 (20.5%)	41 (14.9%)	0.361
Pelvic prolapsus³	65 (27.5%)	28 (10.1%)	0.001	16 (31.4%)	28 (10.1%)	0.001	27 (26.5%)	28 (10.1%)	0.001	22 (26.5%)	28 (10.1%)	0.002
UDI-6*1	28.6±16.9	9.0±9.9	0.001	26.4±18.2	9.0±9.9	0.001	28.1±12.0	9.0±9.9	0.001	33.6±19.6	9.0±9.9	0.001
IIQ-7*2	37.3±24.3	13.3±3.2	0.001	26.1±22.7	13.3±3.2	0.001	40.4±18.6	13.3±3.2	0.001	40.4±29.3	13.3±3.2	0.001

*Mean ± standard deviation, ¹Independent samples t-test, ²Mann-Whitney U test, ³Chi-square test, BMI: Body mass index, DM: Diabetes mellitus, UDI-6: Urinary Distress Inventory Questionnaire, IIQ-7: Incontinence Impact Questionnaire, UI: Urinary incontinence, SUI: Stress urinary incontinence, UUI: Urge urinary incontinence, MUI: Mixed urinary incontinence

Table 3. Multivariable regression analysis

	UI		SUI		UUI		MUI	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age*	0.97 (0.54-1.75)	0.92	0.26 (0.05-1.33)	0.11	1.10 (0.53-2.30)	0.80	1.36 (0.60-3.28)	0.47
BMI**	3.72 (2.43-5.71)	0.01	3.78 (1.90-7.51)	0.01	3.00 (1.73-5.22)	0.01	5.24 (2.94-9.33)	0.01
DM	1.34 (0.74-2.40)	0.33	0.42 (0.10-1.78)	0.25	1.84 (0.91-3.74)	0.09	1.12 (0.51-2.50)	0.78
Menopause	1.36 (0.64-2.90)	0.42	1.42 (0.66-3.02)	0.37	1.59 (0.86-2.94)	0.14	1.76 (0.90-3.42)	0.10
Number of deliveries***	0.92 (0.61-1.38)	0.68	1.51 (0.73-3.10)	0.27	0.91 (0.53-1.55)	0.74	0.40 (0.53-1.36)	0.33
Abortus	1.38 (0.94-2.15)	0.13	1.55 (0.76-3.17)	0.23	0.76 (0.43-1.35)	0.36	2.43 (1.36-4.35)	0.01
History of difficult labor	1.89 (1.15-3.12)	0.02	1.45 (0.64-3.27)	0.37	2.22 (1.22-4.06)	0.01	1.55 (0.73-3.30)	0.26
Pelvic prolapsus	3.22 (1.88-5.51)	0.01	3.90 (1.72-8.84)	0.01	3.37 (1.68-6.73)	0.01	3.38 (1.51-7.55)	0.01

*Under and over 65 years old, **Under and over 30 years old, ***0, 1, 2, 3 years and older, BMI: Body mass index, DM: Diabetes mellitus, UI: Urinary incontinence, SUI: Stress urinary incontinence, UUI: Urge urinary incontinence, MUI: Mixed urinary incontinence

women contributes to the resolution of a health problem which has been ignored so far.

The effect of advancing age on incontinence is still under investigation. Stephan and Hajar (9) claimed that UI was an under-diagnosed and under-treated disorder with deteriorated quality of life in elderly population. In another study, Othman et al. (10) were faced with 24.4% UI rate in women with 25-34 years and 32.3% UI rate in women with 55-64 years. Also, they reported that only aging was a risk factor in the development of UUI and MUI, not SUI. Similarly, it was found that age was significantly older in patients both with UI and UUI and MUI subtypes in univariate analysis. However, multivariable regression analysis revealed that age was not a risk factor in the development of SUI, UUI and MUI in the present study. The mean age was 49.3 years in our study which was a younger average than the average of other studies and that may have had a role on the outcome we came up with.

In obese patients, patients with chronic insulin resistance, increased abdominal pressure and oxidative stress may have a role in the development of UI. Mishra et al. (11) evaluated the relation between obesity and UI and they concluded that higher BMI was associated with SUI and severe UI in middle aged female patients. Also, authors did not find statistically significant correlation between higher BMI and UUI. In parallel with this, Khullar et al. (12) investigated the incidence of UI in 13.178 women and they found a significantly higher SUI rate in the obese patients. Similarly, UI, SUI and MUI were statistically more common in poorly educated obese women in the present study ($p=0.01$ for each parameter).

Previous reports found a significant positive correlation between diabetes mellitus and UI, especially UUI subtype. Furukawa et al. (13) claimed that peripheral neuropathy and micro-vascular

damage resulted in UUI. According to Danforth et al. (14) incidence of UUI up to was seen in 82% of diabetic patients. In another study by Brown et al. (15), prevalence of UUI was significantly higher in diabetic patients and even patients with impaired fasting glucose. In our study, we found a statistically higher diabetes mellitus rate in poorly educated females with UUI and MUI in univariate analysis, however, multivariable regression analysis showed no effect of diabetes mellitus on the development of UUI and MUI ($p=0.09$ and $p=0.78$).

Squamous cells in lower urinary system had an estrogen receptor and deficiency of estrogen in menopausal status has a role in the development of UI with increasing mucosal atrophy in urinary system and total collagen concentration. Zhu et al. (16) reported that the incidence of MUI increased with advancing age and menopausal status. Moreover, according to British cohort study, women in postmenopausal period were reported to have said that their UI complaints were less than pre and perimenopausal women (17). In another study, Rekers et al. (18) reported that MUI was twice more common in postmenopausal women when compared to the ones with premenopausal status. Also, a significant correlation between MUI and postmenopausal status was found in univariate analysis while multivariable regression analysis showed no affect of menopausal status on MUI for poorly educated female population in our study.

What's more, pelvic floor muscle function has a crucial role in preventing UI and it's well known that pelvic traumas such as pelvic surgeries, deliveries, abortus and difficult labor are related to pelvic floor muscle dysfunction. Wu et al. (19) reported that abortus history and number of cesarean sections were predictive factors for UI in women aged 20 years and older. In another study, Onur et al. (20) found that presence of difficult labor

history increased the UI development 1.57 times. In present study we were faced with significantly higher abortus numbers in MUI and difficult labor in women with UUI.

Pelvic organ prolapses and UI, especially SUI subtype, are commonly diagnosed together. Obesity, increased abdominal pressure, lack of hormonal supplement and urogenital trauma may contribute to the development of pelvic organ prolapse and SUI. Islam et al. (21) investigated the predictive factors for UI in women and they found that pelvic organ prolapse was related to MIU (AOR 3.40, 95% CI 2.00-5.80; $p < 0.0001$), and SUI (AOR 2.46, 95% CI 1.34-4.52; $p = 0.004$). In parallel, Okonkwo et al. (22) analyzed incontinence status of 3963 women and they found a strong correlation between UI and pelvic organ prolapse. Also, in present study, multivariable regression analysis revealed that pelvic organ prolapse was significantly related to SUI, UUI and MUI ($p = 0.01$ for each parameter).

The present study had some limitations, though. Cross sectional nature of study without follow up results and absence of treatment outcomes were accepted as limitations in our study. Secondly, period of UI was not examined. Additionally, participants were evaluated by different physicians in three different academic centers. However, to achieve higher internal validity, all physicians were made to undergo the very same education program before the study had started.

CONCLUSION

All in all, our study revealed that the incidence of UI was very high in poor educated female population and higher BMI, presence of difficult labor, pelvic prolapse were risk factors for UI and UUI. Presence of DM and pelvic organ prolapse were the risk factors for SUI. Moreover, higher BMI, abortus numbers and pelvic organ prolapse were significantly related to MUI. The results of our study, though, must be supported by further randomized studies with larger patient volumes and a prospective nature.

Ethics

Ethics Committee Approval: Haseki Training and Research Hospital Ethics Committee (4532771-432).

Informed Consent: Form was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.Y.Ö., Design: F.Ö., Data Collection or Processing: M.E., Ş.B.İ. M.B., Ö.S., Analysis or Interpretation: B.Y.Ö., F.Ö., Ö.S., U.Ç., Literature Search: Ş.B.İ., U.Ç., M.B., Writing: B.Y.Ö., F.Ö.

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Comparison of Neutrophil to Lymphocyte Ratio in Obstructive Sleep Apnea Syndrome Phenotypes

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Abstract

Objective: Our aim in this study was to compare the neutrophil to lymphocyte ratio (NLR) in rapid eye movement (REM) related obstructive sleep apnea (RRO) syndrome (OSAS) and position related OSAS (SRO) to habitual snorers (HSN) and try to find out the phenotype that increases the physical stress more.

Methods: The patient charts and polysomnograms of all subjects referred to Yedikule medical center for chest diseases sleep department between June 2019 and January 2020 were reviewed and classified as RRO, SRO and HSN. Fasting blood tests were performed in the morning following polysomnography. The phenotypes of OSAS were compared to each other by means of NLR.

Results: A total number of 147 cases were reviewed. Forty eight cases were SRO, 49 cases were RRO and 50 were simple snorer. The NLR in RRO was statistically significant from those of SRO and HSN subgroups ($p=0.001$), whereas NLR in groups SRO and HSN were identical ($p=0.650$). Apnea Hypopnea index and O_2 nadir in all groups were statistically significant from each other.

Conclusion: Our data suggests that the REM related OSAS increases NLR as a predictor of inflammation, but NLR stays constant in Position related OSAS and simple snorers.

Keywords: Obstructive sleep apnea syndrome, REM sleep, supine position, snoring

INTRODUCTION

Obstructive Sleep Apnea syndrome (OSAS) is a sleep breathing disorder that has potential cardiovascular and/or neurologic complications. The most prominent feature of OSAS is apnea or hypopnea that decreases or blocks the upper airway passage. OSAS is a complex disease; recent studies suggested certain phenotypes for OSAS; those phenotypes result from the combination of the genotype of the susceptible individual and the environmental effects. Up-to-date, the most common phenotypes of OSAS are named to be rapid eye movement (REM)-related OSAS (RRO) as a result of hyporesponsive genioglossal muscle activity that results in hypopharyngeal blockage of the airway by the tongue base during the REM period and secondly supine related OSAS (SRO)

phenotype that restricts patients sleeping in the supine position (1).

OSAS may generally be attributed as an inflammatory disorder because of its physical load of distress due to hypoxia/hypoxemia and increased effort to breathe (2). Neutrophil to lymphocyte ratio (NLR) is a frequently used marker for subclinical inflammation. Basically, the blood drawn peripherally is used and the number of neutrophils is divided by the number of lymphocytes. Under physiologic stress, by the catalysing effect of the endogenous cortisol and catecholamines, the neutrophils increase and lymphocytes decrease. Normally, NLR in healthy adults are between 1 and 3. However, a mild inflammatory response increases the NLR to 6-9, whereas critically ill patients



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will often have an NLR of 9 or higher, occasionally reaching values close to 100 (3,4).

NLR has been studied in vast areas of medicine including sleep medicine. It has been shown that OSAS induces physical stress that raises the inflammatory markers such as fibrinogen, C-reactive protein (CRP) and NLR (5). However, to the best of our knowledge the phenotypes of OSAS are not studied nor compared to each other.

Our aim in this study is to compare the NLR in RRO and SRO to habitual snorers (HSN) and try to find out the phenotype that increases the physical stress more.

METHODS

This was a retrospective study performed in a tertiary care referral center. The ethical approval was granted from the Ethical Committee of Okmeydanı Training and Research Hospital on 21.01.2020 (48670771-514.10). Informed consents were taken from each and every case. The patient charts and polysomnograms of all subjects referred to Yedikule medical center for chest diseases sleep department between June 2019 and January 2020 were reviewed and classified as RRO, SRO, HSN or unclassified OSAS. Unclassified OSAS was referred to as OSAS that has Apnea Hypopnea index (AHI) greater than 5 events/h but not has any specific feature related to REM stage of the sleep nor worsens due to supine position. For being beyond the scope of this study, unclassified OSAS cases were excluded from the study.

Adequate sample size formulation for the study was calculated as follows;

$$n = \frac{Nt^2pq}{d^2(N-1) + t^2pq}$$

where;

N: Sample size in the universe (Frequency of patients been treated in our clinic within one month)

n: The desired sample size

p: The frequency of occurrence (OSAS incidence was accepted as 7%)

q: The frequency of non-occurrence

t: t value

d: Absolute precision or accuracy, normally set at 0.05

$$n = \frac{(8000)(1.96)^2(0.07)(0.93)}{(0.05)^2(8000-1) + (1.96)^2(0.07)(0.93)} = 98$$

This equation showed that 98 cases or more were adequate for sampling, and our cases were above this value.

Full-night attended polysomnograms including sixteen channel electroencephalography, two channel electrooculography, submental and left/right anterior tibial electromyography (EMG), right/left biceps surface EMG, body position probe, electrocardiography, oro-nasal 4 thermal sensor, nasal pressure sensor, breath sound recording, thoracic and abdominal sensors, pulse oxymeter and synchronous video recordings were recorded. Wake-sleep patterns and sleep related abnormal breathing events were scored with respect to the criteria of American Academy of Sleep Medicine 2017 (AASM). All polysomnograms were evaluated due to AASM-International Classification of Sleep Disorders international sleep diseases 2014 criteria. PSG recordings of all subjects were scored by a sleep expert who was blinded to blood test results of the cases.

As a routine, fasting blood tests were performed in the morning following polysomnography. Detailed parameters included complete blood count, blood glucose, urea, liver function tests, fibrinogen, erythrocyte sedimentation rate, CRP, ferritin and iron levels.

Exclusion criteria included as follow: pediatric age group, subjects other than sleep disordered breathing problems (i.e. insomnia, parasomnia, circadian rhythm disorders, etc.), previous upper airway surgery, any kind of central sleep apnea, upper airway neoplasm and acute rhinitis resulting in nasal obstruction at the time of the study. Obstructive apnea was defined as the total cessation of airflow for ≥ 10 s with continued respiratory effort. Obstructive hypopnea was defined as an event lasting ≥ 10 s that was associated with both a decrease in airflow of 50% and an EEG arousal or oxygen desaturation $\geq 4\%$. AHI was defined as the number of apneic and hypopneic events per hour of sleep.

The predominance of disordered breathing during REM sleep was accepted as: (a) an AHI of nonREM sleep stage fewer than 5 events/h and (b) an AHI of REM sleep stage of at least 5 events/h with at least 30 minutes of REM sleep. If the amount of REM sleep was less than 30 minutes, estimates of AHI_{REM} were considered imprecise and the cases were excluded (6). The predominance of disordered breathing during supine position sleep was accepted as: (a) Overall AHI is greater than 5 events/h, (b) The supine AHI is greater than two times the non-supine AHI and, (c) Non-supine

AHI is less than 5 events/h (7). Habitual (simple) Snorers were defined as snorers with an AHI <5 events/h.

Statistical Analysis

Statistical analyses were performed by SPSS 22.0 (IBM, Turkey). A power analysis revealed our sample size to be adequate for the study. A Shapiro-Wilks test was used to control the normal distribution of the variables. Continuous variables were analyzed by one-way variance analysis test and inter-group comparisons were performed by Post-Hoc Bonferroni tests. Continuous variables were expressed as mean, standard deviation, minimum, maximum and categorical variables as frequency and percentage. A p value of <0.05 was accepted statistically significant.

RESULTS

A total number of 147 cases were reviewed. Forty eight cases were SRO (32.65%; 36 male, 12 female), 49 cases were RRO (33.33%; 28 male, 21 female) and 50 were simple snorer (34.01%; 27 male, 23 female). Descriptive variables are presented in Table 1.

The NLR in RRO was statistically significant from those of SRO and HSN subgroups ($p=0.001$); RRO had the highest value as

of 2.76, SRO had 1.53 and HSN had the lowest value as 1.37. The Post-Hoc values between RRO and HSN was significant ($p=0.001$), however NLR difference in HSN and SRO ($p>0.005$) or SRO and RRO ($p>0.005$) were not significant. AHI and O_2 nadir in all groups were statistically significant from each other as SRO 16.6; RRO 10.1 and HSN 2.3. Also the Post-Hoc values of AHI was statistically significant between RRO and HSN being worse for RRO ($p=0.001$), HSN and SRO, being worse for SRO ($p=0.001$), and SRO and RRO, being worse for SRO ($p=0.005$) (Table 2, Figure 1).

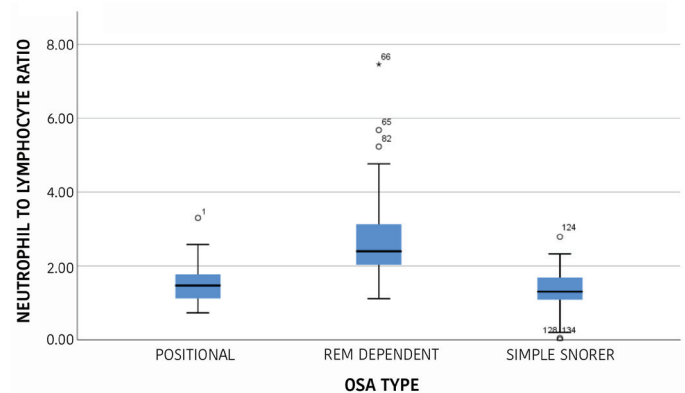


Figure 1. Simple Boxplot of neutrophil to lymphocyte ratio by OSA type OSA: Obstructive Sleep Apnea

Table 1. Descriptives according to OSAS phenotypes

One-way ANOVA		n	Mean	Standard deviation	Minimum	Maximum
Age	SRO	48	45.93	10.18	25.00	66.00
	RRO	49	48.71	10.37	25.00	74.00
	HSN	50	45.32	10.79	25.00	74.00
BMI	SRO	48	30.79	3.93	25.00	41.00
	RRO	49	31.95	7.03	22.00	50.00
	HSN	50	30.20	4.79	21.00	41.00
NLR	SRO	48	1.53	0.55	0.73	3.30
	RRO	49	2.76	1.25	1.12	7.46
	HSN	50	1.37	0.54	0.01	2.79
TST	SRO	48	411.77	45.12	275.00	530.50
	RRO	49	406.02	57.49	230.50	481.00
	HSN	50	386.34	61.25	213.00	528.00
AHI	SRO	48	16.61	9.58	5.70	39.50
	RRO	49	10.10	4.01	5.40	21.70
	HSN	50	2.30	1.33	0.00	4.90
Oxygen nadir	SRO	48	88.33	4.83	77.00	97.00
	RRO	49	84.75	7.49	56.00	96.00
	HSN	50	92.58	3.16	85.00	97.00

OSAS: Obstructive Sleep Apnea syndrome, SRO: Position related OSAS, RRO: Rem related OSAS, HSN: Simple (habitual) snorer BMI: Body-mass index, NLR: Neutrophil to lymphocyte ratio, TST: Total sleep time, AHI: Apnea Hypopnea index, N: Sample size in the universe

Table 2. Multiple comparisons			
Bonferroni			
Variable			p value
Age	SRO	RRO	0.579
	RRO	HSN	0.326
	HSN	SRO	1.000
BMI	SRO	RRO	0.872
	RRO	HSN	0.326
	HSN	SRO	1.000
NLR	SRO	RRO	0.001*
	RRO	HSN	0.001*
	HSN	SRO	1.000
TST	SRO	RRO	1.000
	RRO	HSN	0.234
	HSN	SRO	0.072
AHI	SRO	RRO	0.001*
	RRO	HSN	0.001*
	HSN	SRO	0.001*
O ₂ Nadir	SRO	RRO	0.005*
	RRO	HSN	0.001*
	HSN	SRO	0.001*

*The mean difference is significant at the 0.05 level. BMI: Body-mass index, NLR: Neutrophil to lymphocyte ratio, TST: Total sleep time, AHI: Apnea Hypopnea index, SRO: Position related OSAS, RRO: Rem related OSAS, HSN: Simple (habitual) snorer

DISCUSSION

OSAS is a chronic disease that has repetitive episodes of upper airway collapse and then relief of the collapse by gasping of the susceptible subject, which in turn causes low-level systemic inflammation in a certain time period. It has been linked to a diverse variety of comorbidities such as cardiovascular diseases, pulmonary diseases, endocrine dysfunctions, and neuropsychiatric problems. The disease, furthermore, also causes hypoxia, asphyxia, respiratory acidosis and hypercapnia, which are due to the reoccurring sleep disruptions and leads to the development of local and systemic inflammation. Chronic inflammation is thought to be the underlying pathogenesis, although the exact physiopathology to those health problems remains unclear. However, the inflammation might be the result or the cause of these pathologies; more commonly a bidirectional relationship is frequently questioned (8).

It has been demonstrated in an animal model that apnea and hypoxemia trigger systemic inflammation by inducing changes in the leukocyte function (9). Under physiologic stress, the number

of neutrophils increases, while the number of lymphocytes decreases. The NLR combines both of these changes.

Previous reports demonstrated that patients with OSAS have higher levels of inflammatory markers such as CRP, neutrophil counts, TNF- α , pro-inflammatory cytokines, interleukin 6, serum amyloid A, and leukocyte adhesion molecules (10,11).

Obstructive sleep apnea repetitively fragments the sleep. This fragmentation and inflammatory response increases the sympathetic neural activity. Elevation of the plasma noradrenaline activates the sympathetic nervous system and elevates the serum cortisol. Once the plasma cortisol level increases, a decrease in the relative concentration of lymphocytes occurs and this low level of lymphocytes worsens the clinical outcome. Neutrophils are the frontiers of the defensive cells of the immune system but an uncontrolled release of toxic substances such as inflammatory cytokines or tissue-damaging enzymes may potentiate the damage to surrounding tissues and increase the inflammatory responses. An increase in the neutrophil count of OSAS patients were shown but the reason why neutrophils are increased in the airways of OSAS patients remains unclear. No matter how different mechanisms could be involved, intermittent hypoxia is thought to be the major factor for this phenomenon (12).

In this study, particular importance is attributed to REM sleep. During the REM sleep; the electrical activity of the brain is similar to being awake when measured by oxygen and glucose metabolism being 11-40% lower in non-REM sleep. Areas of the brain that are active during REM sleep are the opposite of the ones activated during non-REM sleep. Especially, the amygdala is active during REM sleep which is involved in autonomic responses associated with fear and hormonal secretions. Scientific studies of the amygdala have led to the discovery of the location of neurons in the amygdala that are responsible for fear conditioning. Body temperature is not well-regulated which can cause to become uncomfortable with more extreme temperatures. The inhibition of motor neurons causes a complete paralysis of the body and REM sleep is the part of sleep where dreams occur; the brain will often deploy "safety measures" to ensure it isn't disrupted. For example, the sound of an alarm clock or phone may be incorporated into the dream and transformed into something else. All those features associated with REM sleep causes increased heart rate and catecholamines and shallow breath. Additional inhibition of the skeletal muscles increases the apnea/hypopnea events and hypoxemia deepens (13). All abovementioned responses load important stress level to the affected body and the stress levels

gradually increase throughout the evolution of the disease. Those mechanisms were in concordance with our study; the NLR ratio of REM was significantly higher than the other two groups. We accepted RRO to have a REM period equal or greater than 30 minute. However, the time variable was not a constant valid rule for SRO. This might be an important clue to explain why RRO NLR was higher than HSN but SRO was not statistically significant than HSN. If the standardization of the time variable spent in both REM sleep and supine position sleep should be set as 30 minutes, maybe the scores would change and NLR of both OSAS phenotypes might be the same. We believe further researches in the area illuminating this point could be of importance.

CONCLUSION

The literature reviews support the NLR increase in general OSAS, but the phenotypes were not studied before. Our data suggests that the REM related OSAS increases NLR as a predictor of inflammation, but NLR stays constant in Position related OSAS and simple snorers.

Ethics

Ethics Committee Approval: Ethical Committee of Okmeydanı Training and Research Hospital on 21.01.2020 (48670771-514.10).

Informed Consent: Informed consents were taken from each and every case.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.G., C.Ö., Design: B.G., C.Ö., Data Collection or Processing: B.G., B.T., C.Ö., Analysis or Interpretation: B.G., B.T., Literature Search: B.G., B.T., Writing: B.G.

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

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Evaluating the Safety of Sodium Hypochlorite Usage as an Irrigation Solution in Acute Osteomyelitis: an Experimental Study in Rat Tibia via a Renewed Osteomyelitis Model

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Abstract

Objective: The ideal irrigation solution for osteomyelitis surgery has not yet been clarified. The aim of this study is to evaluate the therapeutic effect and the optimum concentration of sodium hypochlorite (NaOCl) solution for the mechanical treatment of acute osteomyelitis.

Methods: Forty tibias of 20 male Wistar rats were used. The medullas were percutaneously inoculated with *Staphylococcus aureus* ATCC 25923 to induce acute osteomyelitis in tibias. One week later, rats were randomly assigned to 3 treatment groups and irrigated with 0.5%, 1% and 5% NaOCl. Irrigation with saline was used at positive control group and any treatment was not given to negative control group. All rats were sacrificed 24 hours after NaOCl irrigation. The degree of bacterial density, necrosis, inflammation and edema were evaluated histologically as; none (0), mild (1), moderate (2) and severe (3). Kruskal-Wallis and Dunn tests were used for statistical evaluations.

Results: Acute osteomyelitis developed in all tibias. NaOCl treatment no matter the concentration reduced the bacterial density compared to negative control group. The decrease in bacterial density and inflammation was significant at 0.5% NaOCl group compared to positive group (respectively; $p=0.019$, $p=0.045$), while the pairwise comparisons were statistically insignificant in terms of necrosis and edema. There was not any statistically difference between positive and 1%-5% NaOCl groups in terms of bacterial density.

Conclusion: In conclusion, irrigation with 0.5% NaOCl was more therapeutic than saline, 1% NaOCl and 5% NaOCl concentrations for acute tibia osteomyelitis at rats while 0.5% NaOCl group was same with saline group in terms of safety to tissue.

Keywords: Acute osteomyelitis model, experimental animal model, rat, sodium hypochlorite irrigation, treatment

INTRODUCTION

Acute osteomyelitis, a disease of bone due to the infection, rare but serious condition, is great concern in orthopedic surgeries. The most cause of the acute osteomyelitis is the hematogenous

spread of the causative bacteria into the bone, and less cause by surgery as open fracture surgery, or bone surgery including joint replacements/osteosynthesis (1). It develops rapidly over a period of 7 to 10 days, and in some specific situations (i.e. presence of heart failure, immunosuppressant medications) can



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be life treating (1,2). In the treatment, debridement and irrigation with several solutions during the surgery, and antibiotic usage are the first line options with the aim to control and remove the infection (2). The people infected might need to get their antibiotic medications for several weeks and in more serious osteomyelitis, surgery to remove the infected tissue and bone might be required.

The irrigation with solutions is commonly performed in orthopedic surgeries to keep patient from risk of infection. Isotonic saline, disinfectants or antibiotic solutions may be used as irrigation solution (3-6). In most circumstances saline is preferred for the irrigation of surgical site but it does not have any effect on microorganisms (4). The usage of antibiotic solutions is very limited because of its higher cost and antibiotic resistance but disinfectants remain as an option (4). The appropriate solution for irrigation has not been clarified thus far (2). Owing to rising antibiotic resistance in recent years, the importance of irrigation solutions has increased further (1). This, in turn, has revealed the importance of the antimicrobial effects of irrigation solutions (2).

To perform a most proper treatment for acute osteomyelitis, animal studies are done by using foreign body (7). Because the difficulty of performing infection at rats, the majority of osteomyelitis performing models use foreign objects as sclerosing material, heat or necrosis (7-9). The common source for acute osteomyelitis is known to be *Staphylococcus aureus* due to hematogenous transmission (1,2). Due to the usage of foreign objects as sclerosing material, heat or necrosis at osteomyelitis models, we think these performed techniques don't reflect exactly the acute osteomyelitis.

Sodium hypochlorite (NaOCl) is common used disinfectant in general purpose and health care services. It has lethal effect on viruses, fungi and wide spread of bacteria, and hence it is used for tap water disinfection (10). NaOCl is reported to be toxic to cell even at very lower concentration (0.01%) *in vitro* (11). Though the *in vitro* studies, in management of dental infections, 0.5% to 5% NaOCl solutions are used for irrigation with success (12-14). However, NaOCl solutions are not routinely used as an irrigation solution for osteomyelitis surgeries.

In the present study, we aimed to investigate the safety and the efficacy of different concentrations (0.5 to 5%) of NaOCl due to a renewed acute osteomyelitis model of rat tibia.

METHODS

The study was conducted upon the permission of local ethics committee for animal experiments (HADYEK, 15.12.2016,

2016/16). Twenty male Wistar albino rats weighing 200-250 g were used. All animals involved in experiments have received humane care in compliance with the Guide for the Care and Use of Laboratory Animals (15). Rats were fed ad libitum; the temperature was 22+/-2°C with the 50% humidity. The rats were kept at 12/12h dark and light cycles. To prevent unnecessary animal sacrificing, both tibias of all animals were used.

Fluids Used for Irrigation and Creating the Groups

At the surgical processes under anesthesia, 2 rats were died. The remaining 18 rats were randomly divided into 5 groups. The 1st group was the negative control group (group 1) (n=3 rats, n=6 tibias) for which no treatment was applied. The 2nd group was the positive control group (group 2) (n=3 rats, n=6 tibias) which was treated with saline (0.9% NaCl isotonic) as it is routinely used in surgery. The other three groups were treatment groups and were named as; 0.5% NaOCl (group 3) (n=4 rats, n=8 tibias), 1% NaOCl (group 4) (n=4 rats, n=8 tibias) and 5% NaOCl (group 5) (n=4 rats, n=8 tibias). A brief summary of groups and applied treatments are given at Table 1.

Preparation of Bacterial Suspensions

Standard Methicillin-sensitive *Staphylococcus aureus* (MSSA) ATCC 25923 isolate, stored in freezer at -80°C was brought to room temperature and then incubated overnight in 5% sheep's blood agar passaging at 37°C. The next day after purity check of bacteria, bacterial suspensions with McFarland 10 turbidity (approximately 3x10⁹ cfu/mL) were prepared in saline.

Induction of Osteomyelitis and Irrigation

All rats had intraperitoneal ketamine (50 mg/kg) (Ketalar; Eczacıbaşı, İstanbul, Turkey) and xylazine (10 mg/kg) (Rompun; Bayer, Leverkusen, Germany) for anesthesia. Knees were wiped with povidone iodine. Supplemental analgesia was provided by intraperitoneal injection of buprenorphine (0.3 mg/kg). The

Group number	Group name	Number of tibias (n)	Treatment administered
1	Negative control	6	No treatment
2	Positive control	6	Irrigation with 20 mL of saline
3	0.5% NaOCl	8	Irrigation with 20 mL of 0.5% NaOCl
4	1% NaOCl	6	Irrigation with 20 mL of 1% NaOCl
5	5% NaOCl	8	Irrigation with 20 mL of 5% NaOCl

NaOCl: Sodium hypochlorite

tuberositas tibia (TT) was palpated. Percutaneous drilling with a 22-gauge needle tip (without skin incision) from the TT to tibial medulla was performed (16). After drilling, a 26-gauge needle tip was used to inoculate the medulla percutaneously with 10 μ L (nearly 3×10^7 cfu) of the bacterial suspension of *Staphylococcus aureus*. During follow-up, 7.5 mg/kg paracetamol (Parol, Atabay, İstanbul, Turkey) was added to drinking water.

After 7 day of inoculation with bacterial suspension to the rat tibias, experimentations in all groups were performed under ketamine (50 mg/kg)/xylazine (10 mg/kg) anesthesia with buprenorphine (0.3 mg/kg) analgesia. After the knee joints were wiped with povidone iodine, 1 cm longitudinal incision was done to the TT. Using the previous entry point, the tibia medulla was manually drilled with 22-gauge needle tip. At the point where the needle entered the bone, soft tissues were excised to allow fluid flow out of the medulla. Then the tibias in the groups were irrigated with the relevant solutions for 30 seconds. After the irrigation, 4/0 no absorbable polypropylene sutures (Propilen; Doğan Tibbi Malzeme San A.Ş, Trabzon, Turkey) were used to close the skin. At follow-up, rats received 7.5 mg/kg paracetamol ad libitum in drinking water. After irrigation, 1 rat in the 1% NaOCl group died (3 rats died in sum).

Radiological Magnetic Resonance Imaging (MRI) Assessment of Osteomyelitis Induction

On the 7th day of the study, rats were anesthetized intraperitoneally with ketamine (50 mg/kg) and xylazine (10 mg/kg).

To determine whether osteomyelitis developed in rats with tibias inoculated with bacteria or not, contrast (0.1 mmol gadobutrol/kg) T1 MRI (Siemens Magnetom Aera 1.5T, Erlangen, Germany) was used (17). Contrast material was administered intraperitoneally. Thin sagittal sections of the tibia were taken (Figure 1). As tibias without contrast would not be included in the study, a radiologist, and an orthopedist assessed results during imaging.

Histopathology

On the 8th day of the study (24 hours after irrigation), the rats were sacrificed with high doses of ketamine (100 mg/kg) and xylazine (100 mg/kg) anesthesia. Both tibias of rats (total 34) were dissected, including the soft tissues surrounding the tibias, and placed into 10% formalin, and submerged in paraffin. Sagittal sections in 4 μ m thickness were taken with a microtome (Thermo Scientific Microm HM 340E). Paired consecutive sections from each tibia were stained with HE and two were stained with Giemsa. Two different pathologist under a light microscope (Olympus CX41) performed histopathological

assessments in blind. Bone and soft tissues were assessed for necrosis, inflammation, edema and bacterial density. For all assessments, scoring was none (0), mild (1), moderate (2) and severe (3) according to density and spread of the parameter examined (18).

In Vitro Investigation of Antibacterial Activity of NaOCl Against Standard Pathogenic Bacterias

An *in vitro* study was conducted to investigate the effectiveness of the NaOCl available. The aim of this investigation was to evaluate the antibacterial activity of NaOCl against four different standard bacteria with minimal inhibitor concentrations by alamar blue microdilution broth method. The standard obtained from the American type culture collection (ATCC); MSSA ATCC 25923, *Escherichia coli* ATCC 25922, *Salmonella typhimurium* ATCC 14028, *Pseudomonas aeruginosa* ATCC 27853 isolates were used. Serial dilution of NaOCl was carried out in sterile microplates of 96 wells, ranging from 1/2 to 1/1024 in Mueller Hinton Broth (MHB, Merck) medium. Suspensions of standard bacteria (turbidity number 107-108 cfu/mL) adjusted to McFarland 0.5 turbidity were added 100 mL to wells and incubated at 37°C. The last two wells were used as a negative (only medium and NaOCl) and positive (only medium and bacteria) control. After 20 hours, 20 μ L of alamar blue (Sigma-Aldrich, USA) was added to the microplates and incubated for another 4 hours. The change of the alamar blue in the wells to pink color according to the color change was interpreted as the presence of reproduction or the absence of color change was interpreted as stopping the reproduction. In addition, samples were taken from the wells were cultivated and reproduction was

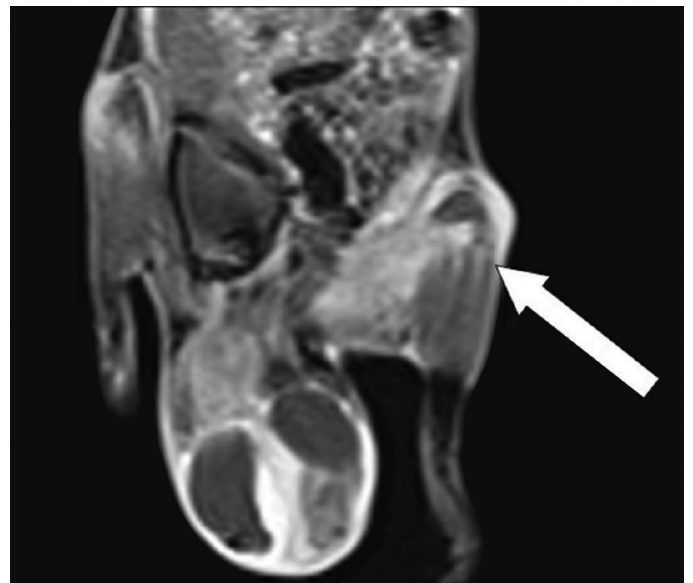


Figure 1. Contrast T1 MRI showing significant contrast enhancement MRI: Magnetic Resonance Imaging

checked. The concentration of stock NaOCl used was 5%. The concentrations were reduced by half and half.

Statistical Analysis

Statistical analyses were performed using R 3.5.1 Statistical Software (r-project), a free software environment for statistical computing and graphics. ICC estimates and their 95% confidence intervals were calculated using SPSS statistical package version 17.0 (SPSS Inc, Chicago, IL) based on a mean-rating (k=2), consistency and 2-way random-effects model. ICC values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 were indicative of poor, moderate, good, and excellent reliability, respectively (19).

The variables in the study were measured at an ordinal level thus the baseline characteristics of the groups were presented as median and interquartile range. The Kruskal-Wallis test was used as an omnibus test to compare medians of groups (20). Dunn multiple comparison test (21) was used after significant Kruskal-Wallis test (20). DunnTest function in FAS package of the R program was used for multiple comparisons. P values adjusted with the False Discovery Rate method were given.

RESULTS

Comparing the two observers to one another, the intra class correlation for edema, inflammation and necrosis were 0.90 (95% confidence interval (CI): 0.77-0.912), 0.914 (95% CI: 0.754-0.981) and 0.843 (95% CI: 0.617-0.940), respectively.

It was of interest to test whether there was a significant difference among negative control, positive control, 0.5% NaOCl, 1% NaOCl, and 5% NaOCl groups in terms of necrosis, inflammation in soft tissues and bones, edema in soft tissues, and bacterial density in bones. Descriptive statistics of variables for each group and the associated p values of the Kruskal-Wallis tests are shown in Table 2. Significant differences were found between the groups in terms of inflammation in soft tissues, necrosis, inflammation and bacterial density in bones with p values of 0.0241, 0.0239,

0.00022 and <0.001, respectively (Table 2). The adjusted p values of post hoc tests are shown in Table 3.

Percutaneous *Staphylococcus Aureus* Inoculation to Rat Tibias Caused Acute Osteomyelitis

With the percutaneous bacteria inoculation method, we identified the success rate for acute tibial osteomyelitis to be 100% in rat tibias. Investigated with contrast T1 MRI, 34 tibias of 17 rats were identified to have acute osteomyelitis. Contrast material involvement was observed in all of the 34 tibia medullas and in soft tissues surrounding tibias (Figure 1). After sacrificing; necrosis, acute inflammation and edema in surrounding soft tissues, bone marrows and soft tissues in all tibias with HE staining, and bacterial colonization with Giemsa staining were observed in histopathological investigations.

Irrigation with NaOCl Reduced Bacterial Density

While the density of bacteria was assessed histopathologically with Giemsa staining, a variety of dimensions and densities of bacterial colonization were observed and classified (Figure 2). Significant differences were found between groups in terms of bacterial density in bones. No significant differences were found between negative and positive control groups in pairwise comparisons (p=0.388) (Table 3). The 0.5% NaOCl, 1% NaOCl and 5% NaOCl groups had significantly lower amount of bacterial density in bones than that of the negative control group (negative control vs. 0.5% NaOCl, p<0.001; negative control vs 1% NaOCl, p=0.039; negative control vs 5% NaOCl, p<0.001). The 0.5% NaOCl group had a significantly lower amount of bacterial density in bones than that of the positive control group (Table 3) (positive control vs 0.5% NaOCl, p=0.019). The 1% NaOCl and 5% NaOCl groups had no significant difference compared to the positive control group (Table 3) (positive control vs 1% NaOCl, p=0.192; positive control vs 1% NaOCl, p=0.186).

These findings show that NaOCl usage reduced the density of bacteria. With 0.5% NaOCl usage, bacterial density was significantly reduced compared to the positive control group.

Table 2. Descriptive statistics and Kruskal-Wallis test results

		Negative control	Positive control	0.5% NaOCl	1% NaOCl	5% NaOCl	Test statistic (p)
Bone marrows	Bacterial density	3 (0)	2 (0.75)	1 (0.25)	2 (0.75)	1 (0)	25.7 (<0.001*)
	Necrosis	2 (0)	1 (0.75)	1 (0.25)	1.5 (1)	2 (0)	12.95 (0.02*)
	Inflammation	3 (0)	2.5 (1)	2 (0)	2 (0)	2 (0)	18.66 (0.002*)
Soft tissues	Necrosis	1 (0.75)	1 (0.75)	0 (0.25)	0.5 (1)	1 (1.25)	4.49 (0.48)
	Edema	2 (0)	2 (0)	2 (1)	2 (0)	2 (0.25)	7.06 (0.21)
	Inflammation	3 (0.75)	3 (0)	2 (0.5)	2 (0.75)	2 (0)	12.9 (0.02*)

Data are expressed as median with interquartile range in parentheses, NaOCl: Sodium hypochlorite, *p<0.05

Irrigation with NaOCl Reduced Inflammation

Inflammation was assessed with HE staining. During assessment of inflammation, neutrophil density in bone marrows was observed to decrease (Figure 3). No significant difference was

found in bone marrows between negative and positive control groups in terms of inflammation ($p=0.383$) (Table 3). The 0.5% NaOCl, 1% NaOCl and 5% NaOCl groups had significantly lower amounts of inflammation in bone marrows than that of the

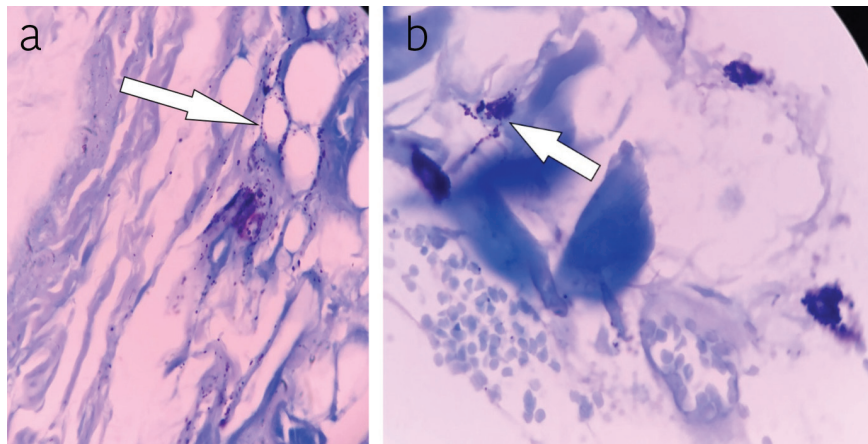


Figure 2. Bacterial density (Giemsa staining, 40x100 magnification). Arrows indicate the bacteria; a) 0.5% NaOCl group, score 1, b) positive control group, score 3

NaOCl: Sodium hypochlorite

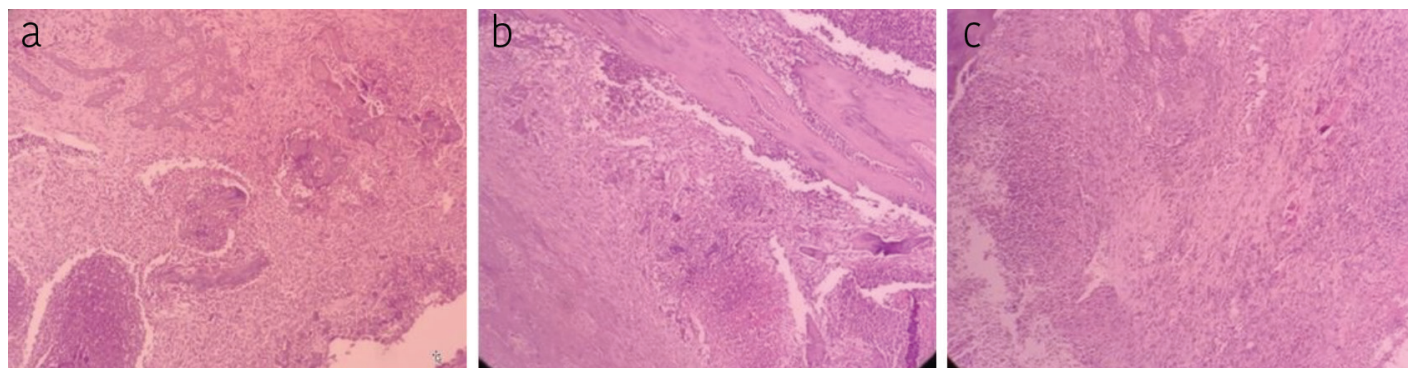


Figure 3. Inflammation and necrosis of soft tissues and bones (H & E 10x100); a) 0.5% NaOCl (irrigation with 0.5% NaOCl), necrosis score 1, inflammation score 3, b) positive control (irrigation with saline, necrosis score 1, inflammation score 2, c) negative control (no irrigation) necrosis score 2, inflammation score 3

NaOCl: Sodium hypochlorite, H & E: Haematoxylin and eosin

Table 3. Multiple comparisons for significant tests (adjusted p values)				
Comparison	Bacterial density in bones	Necrosis in bone marrows	Inflammation in bone marrows	Inflammation in soft tissues
Negative control - positive control	0.388	0.108	0.383	0.575
Negative control - 0.5% NaOCl	<0.001	0.086	0.011	0.182
Negative control - 1% NaOCl	0.039	0.334	0.045	0.511
Negative control - 5% NaOCl	<0.001	0.891	0.036	0.189
Positive control - 0.5% NaOCl	0.019	0.964	0.094	0.045
Positive control - 1% NaOCl	0.192	0.555	0.285	0.153
Positive control - 5% NaOCl	0.186	0.081	0.325	0.031
0.5% NaOCl - 1% NaOCl	0.326	0.528	0.727	0.650
0.5% NaOCl - 5% NaOCl	0.703	0.076	0.549	0.914
1% NaOCl - 5% NaOCl	0.209	0.252	0.872	0.674

NaOCl: Sodium hypochlorite

negative control group (negative control vs 0.5% NaOCl, $p=0.011$; negative control vs 1% NaOCl, $p=0.045$; negative control vs 5% NaOCl, $p=0.036$) (Table 3). No significant difference was found in terms of inflammation in bone marrows between the positive control group and 0.5% NaOCl, 1% NaOCl and 5% NaOCl groups (positive control vs 0.5% NaOCl, $p=0.094$; positive control vs 1% NaOCl, $p=0.285$; positive control vs 5% NaOCl, $p=0.325$) (Table 3).

In assessment of inflammation, neutrophil density in soft tissues was observed to decrease. No significant difference was found in soft tissues between negative and positive control groups in terms of inflammation ($p=0.575$) (Table 3). Also no significant difference was found in soft tissues in terms of inflammation between negative and 0.5% NaOCl, 1% NaOCl, and 5% NaOCl groups (negative control vs 0.5% NaOCl, $p=0.182$; negative control vs 1% NaOCl, $p=0.511$; negative control vs 5% NaOCl, $p=0.189$). The 0.5% NaOCl and 5% NaOCl groups had significantly lower amounts of inflammation in soft tissues compared to the positive control group (positive control vs 0.5% NaOCl, $p=0.045$; positive control vs 5% NaOCl, $p=0.031$) (Table 3).

With these findings, it is possible to suggest that irrigation of osteomyelitis with NaOCl reduces inflammation in bone marrows and soft tissues in osteomyelitis disease.

Soft Tissue Edema and Necrosis Rates were Comparable in Each Group

Edema in soft tissues was assessed with the increase in intercellular space and neutrophil infiltration. No difference was observed between the groups. When groups were assessed in terms of soft tissue edema, no statistical difference was observed ($p=0.21$) (Table 2).

In all groups, necrosis was observed in bone marrows and lamellar bones along with soft tissues (Figure 3). Although, a significant difference was found between the groups with respect to necrosis in bone marrows (Table 2) ($p=0.02$), pairwise comparisons could not detect any pairwise significant difference at the 0.05 significance level ($p>0.05$) (Table 3). Thus, it can be concluded that the groups did not differ in terms of necrosis in bone marrows ($p>0.05$) (Table 3). There was no difference observed between the groups in terms of necrosis in soft tissues also (Table 2) ($p=0.48$). These findings show irrigation of osteomyelitis with NaOCl did not increase necrosis in bone marrows and soft tissues.

In Vitro Results of Antibacterial Activity of NaOCl Against Standard Pathogenic Bacterias

Briefly the *in vitro* results were given at Figure 4. The 1/64 (0.078% NaOCl) dilution of NaOCl was effective against all bacteria other

than *Escherichia coli*. The dilution of NaOCl at 1/128 (0.039% NaOCl) was effective against *Escherichia coli*.

DISCUSSION

Previously, many experimental osteomyelitis models have been described and any foreign material is used to perform osteomyelitis models in rats (7,22,23). Acute osteomyelitis in humans is generally observed with the hematogenous route without presence of foreign objects. With the aim of simulating the completely acute osteomyelitis scene, we did not use foreign objects in the acute osteomyelitis induction model unlike the osteomyelitis models which were performed by using foreign materials as bone wax, sclerosing agents, K wires etc. (7,22,23). The standard MSSA ATCC 25923 isolate was used as it is the most common pathogen associated with implants and is successful in inducing infections (24,25). The dose used for bacterial inoculation was above the minimal required dose (10^7 CFU) recommended by Worlock et al. (26). During preliminary studies, before beginning the experiment, the drilling and bacterial inoculation procedure were applied with an incision above the TT. However, in this preliminary study, the inoculated bacterial suspension drained out of the bone medulla through the hole which we drilled for needle entry, before we could close the hole by bone wax. We predicted the reason for this drainage was the pressure of intramedullar hemorrhage formed in the tibias. Therefore, we chose the percutaneous method as a research technique, and drilled the tibias percutaneously similar to the method Rissing et al. (16). used sclerosing agents at rats but we did not use sclerosing material as Gaudin et al. (27) method that performed at rabbits, with the concerns of not using foreign material to mimic the acute osteomyelitis model more exactly. Additionally, as there was no skin incision in our percutaneous



Figure 4. The *in vitro* results of NaOCl against 4 different bacterial pathogens. The used stock NaOCl concentration was 5%. The concentrations of in the *in vitro* investigation were reduced half and half

NaOCl: Sodium hypochlorite

technique, there was no need to use foreign materials like bone wax to close the hole formed in the bone. T1 contrast MRI taken 1 week after bacterial inoculation revealed contrast involvement in all tibias and soft tissues surrounding the tibias (Figure 1) (17). Histopathologically, osteomyelitis was observed in all tibia sections (Figure 2). Previously described methods have reported lower osteomyelitis development rates as 90% (7,24). The probable reasons for developing acute osteomyelitis at all tibias in the present study may include 1) success of the bacterial strain (MSSA ATCC 25923) inoculated into the medulla for inducing infections (24), 2) applying bacterial inoculation above the required minimum dose (10^7 CFU) for osteomyelitis development (26), and 3) keeping all of the bacterial suspension within the tibia medulla thanks to percutaneous inoculation.

As commonly known, NaOCl has cytotoxic effects. Therefore, whether the possible necrosis we could observe at results was due to the cytotoxic effect of NaOCl or the drill technique we applied was one of our major concerns. It is well known that high torque drilling or using motors perform necrosis because of heat effect (9). So, attempts were made to standardize the irrigation procedure because of the potential necrosis performing of the drilling method. Before the irrigation procedure, all tibias were kindly and slowly pitted with an 18-gauge needle tip and irrigation solutions were administered intramedullary by using a 22-gauge needle tip. The present study did not identify a significant difference in terms of necrosis of soft tissues ($p=0.48$) (Table 2) and bone marrows ($p>0.05$) (Table 3) between the groups (Figure 3). The lack of difference for bone marrows and soft tissues in the groups in terms of necrosis abides by the principle of "not harming the tissue" required for the ideal irrigation solution (2). Besides, at our preliminary study which we compared the saline and NaOCl irrigation in terms of necrosis and safety after drilling the tibia, there was not any difference between saline and 0.5% NaOCl groups (unpublished data). So we think, unlike the osteomyelitis methods those use high torque motors to perform necrosis (9), current low torque drilling method made by manually did not cause additional necrosis.

The importance of acute osteomyelitis due to orthopaedic implants is increasing worldwide. The treatment of acute and chronic osteomyelitis is different from each other. The irrigation of the infected area accelerates the improvement (28). Besides if there is an implant at the body, the most important criteria was the time after the implantation surgery for the differential diagnosis of acute/chronic infection. If the time after the implantation was more than one year, the case was accepted as chronic infection. But currently the most important criteria

are the time to start the complaints up to 3 weeks (29). To apply surgery and irrigation at the treatment of implant related acute infections, the irrigation solution gains more important (28).

Different solutions are commonly used in clinical practice, in order to irrigate the orthopedic infections during the surgery (3-6). Saline and castile soap solution were compared for irrigation of open fractures, the saline was found to be more effective (30). Azzam et al. (31) found 44% success with the application of antibiotic serum irrigation for patients with infected prosthesis. George et al. (5) recommended the irrigation with chlorhexidine in order to prevent infection in total joint prosthesis. Dakin's solution, contains 0.5% NaOCl, is used in diabetic foot and osteomyelitis treatments (6,32,33). Before the widespread use of antibiotics, Dakin's solution is used for the continuous irrigation-suction treatment method for chronic osteomyelitis (6,34). We investigated the NaOCl, because the NaOCl has the advantage of effectiveness on all resistance bacteria, viruses, prions and fungi compared to other disinfectant (10). In the *in vitro* part of the current study NaOCl is germicidal even at lower concentrations (Figure 4). As NaOCl with concentrations from 0.5% to 5% are used for treatment purposes in humans (12-14,32,33), we researched this concentrations interval for irrigation of acute tibial osteomyelitis in the current study.

There are numerous *in vitro* studies with different irrigation solutions in the presence of infection (35-37). Van Meurs et al. (36) recommended povidone iodine as the ideal irrigation solution in an *in vitro* study. Usage of chlorhexidine with orthopedic implants was shown to reduce biofilm formation *in vitro* (37). Ernest et al. (35) reported that NaOCl reduced biofilm and bacterial concentration via *in vitro* studies. The suggested concentrations of NaOCl at *in vivo* (6,32-33) and *in vitro* (11,35,38,39) studies are different each other. The suggested concentrations of NaOCl is lower (0.01 NaOCl) at *in vitro* (11) studies than *in vivo* and human (0.5-5% NaOCl) (6,12-14,32,33) studies. This is most probably because of the lack of defense system of living organism, as white blood cell, macrophages, immune system, hormones etc, at *in vitro* conditions.

Irrigation alone is not sufficient for osteomyelitis treatment (40). However, it is an important stage in surgery. The criteria (2) for the ideal irrigation fluid are as follows: 1) It should reduce the number of pathogens mechanically by irrigating the surgical site 2) it should reduce the number of pathogens by antimicrobial effect 3) it should not cause side effects such as damaging the tissues. In our study we found: 1) Soft tissue (Table 2) and bone marrow (Table 3) necrosis were insignificant between the groups, abiding by the lack of harm condition for the ideal irrigation

fluid, 2) the reduction in bacterial density with the use of NaOCl abides by the condition of reducing the density of bacteria mechanically and through antimicrobial effect, and 3) the reduction of inflammation in soft tissues and bones with the use of NaOCl may be interpreted as NaOCl to be a marker that regresses the disease. This study revealed the histological results of NaOCl irrigation in acute osteomyelitis of the long bones.

In terms of treatment efficacy, the most important aspect of this study was the decrease in bacterial density. When compared with the negative control group, all three NaOCl groups were observed to have significantly reduced bacterial density ($p < 0.001$, $p = 0.039$ and $p < 0.001$, respectively) (Table 3). When NaOCl groups were compared with the positive control group in terms of bacterial density, only the 0.5% NaOCl group had a significant reduction in bacterial density ($p = 0.019$). But when the 1% NaOCl and 5% NaOCl groups were compared with the positive control group in terms of bacterial density, no statistical difference was observed ($p = 0.192$, $p = 0.349$ and $p = 0.186$, respectively) (Table 3). Higher concentrations of NaOCl can be predicted to be more bactericidal. But this situation is in accordance with the literature; it is known that lower concentration of alcohol is more bactericidal than that of higher concentrations (41,42). A recently study made by our study group revealed that H_2S , a toxic hormone at higher concentrations, can be therapeutic at physiological low doses (43). Besides, Wong and Cheung (44) applied 0.5% and 3% concentrations of NaOCl for irrigation and searched for bacterial density in an *ex vitro* study made with extracted human teeth. The 0.5% NaOCl and 3% NaOCl groups were found to be statistically insignificant in reducing bacterial density. In our study, statistically compared with both the negative and positive control groups, the only treatment group that significantly reduced bacterial density was the 0.5% NaOCl group (Table 3). This feature of 0.5% NaOCl abides by the principle (2) of antimicrobial effect desired in the ideal irrigation solution.

Osteomyelitis does not only affect bone tissues but also the surrounding soft tissues (45). Hence, when bones recover from the disease, soft tissues start to recover as well. We detected inflammation to be reduced in bone marrows ($p = 0.002$) and soft tissues ($p = 0.02$) in the first 24 hours after irrigation of osteomyelitis with NaOCl (Figure 3) (Table 2). This situation may be interpreted as NaOCl irrigation of bone with acute osteomyelitis may have therapeutic effects on bones and surrounding soft tissues.

Based on the results of the first 24 hours, there was no statistical difference identified between the groups in terms of soft tissue edema ($p = 0.21$) (Figure 3) (Table 2). The edema formed by NaOCl

in soft tissues disappears within 24-48 hours in clinic (12). This finding may be assessed as irrigation with NaOCl does not cause additional edema in soft tissues.

CONCLUSION

In conclusion, 1) experimental acute osteomyelitis developed in all tibias by using the percutaneous bacterial inoculation 2) the findings indicate that 0.5% NaOCl is beneficial for irrigation of acute osteomyelitis and there is a need for further studies on the topic.

Ethics

Ethics Committee Approval: The study was conducted upon the permission of local ethics committee for animal experiments (HADYEK, 15.12.2016, 2016/16) Republic of Turkey Ordu University Animal Experiments Local Ethics Committee.

Informed Consent: Animal experiments.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: K.A., C.Z.E., Design: K.A., C.Z.E., Data Collection or Processing: A.D., İ.Ç., F.Y.A., Ş.D., Analysis or Interpretation: C.Z.E., E.A., Literature Search: A.D., F.Y.A., Writing: K.A., S.T., C.Z.E.

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Sarcomatoid Carcinoma of the Urinary Bladder: A Case Report and Review of the Literature

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Abstract

Sarcomatoid variant of urothelial carcinoma of the urinary bladder is a rare malignant neoplasm, which is defined with biphasic neoplasm with both an epithelial and a mesenchymal component by histopathological and immunohistochemistry. It is responsible for 0.3% off all bladder carcinomas. The aim of this study was to present the histopathological and immunohistochemical findings of a case of sarcomatoid carcinoma of the urinary bladder and to review the relevant literature. A 75-year-old man was presented to our hospital with hematuria. 6.5x5.8 cm tumor was found in the urinary bladder at ultrasonography. Magnetic resonance imaging demonstrated a large irregular-shaped 9x5 cm tumor involving the right posterolateral wall of the urinary bladder and an atrophic kidney. The patient underwent cystoprostatectomy, left nephrectomy, and lymph node dissection. Macroscopically, a 7.5x6.1x1.8 cm ulcero-vegetating tumor mass infiltrating the bladder base, right-left side wall, anterior-posterior wall, and trigon was seen. Microscopically, this tumor was composed of high-grade urotelial carcinoma and mesenchymal differentiation areas with a wide eosinophilic cytoplasm, vesicular nucleus, distinct nucleolus and spindle-shaped areas. Immunohistochemically, mesenchymal differentiation areas were stained prominently with vimentin, keratin. The case was diagnosed as sarcomatoid carcinoma. Tumor metastasis was detected in the prostate and in bilateral pelvic lymph nodes. Although the clinical findings and the age of diagnosis of sarcomatoid urothelial carcinoma are similiar to conventional urothelial carcinoma, it has a worse prognosis. The presented case died 2.5 months after surgery. Sarcomatoid carcinoma seems to represent the final common pathway of urothelial carcinoma dedifferentiation. Keeping this aggressive tumor type in mind is essential for a correct treatment approach

Keywords: Urinary bladder, epithelial, mesenchymal, malignant

INTRODUCTION

Sarcomatoid carcinoma of the bladder is a biphasic malignant tumor in which epithelial and mesenchymal differentiation is determined morphologically and immunohistochemically (1). According to the Surveillance, Epidemiology, and End Results (SEER) database of the US National Cancer Institute, this tumor accounts for 0.6% of all bladder tumors (2,3). We presented the clinical, histopathological, and immunohistochemical findings of this tumor, which shows a much more aggressive clinical course compared to urothelial carcinoma, in the light of the literature.

The Case

A seventy-five-year-old male patient applied to our hospital's urology outpatient clinic with a complaint of hematuria. An abdominal ultrasonography revealed a 6.5x5.8 cm mass, filling the bladder. Upon determination of a 9x5 cm mass extending from the right posterolateral wall of the bladder and atrophy findings in the left kidney in the magnetic resonance imaging, the patient underwent cystoprostatectomy, left nephrectomy and pelvic lymph node dissection. No malignancy was observed in the intraoperative consultation of the right ureter lower end surgical margin. Macroscopic evaluation of the bladder



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revealed a 7.5x6.1x1.8 cm ulcero-vegetating mass involving the bladder base, right and left walls, anterior-posterior walls, and the trigon. The sections of the mass were grayish in color and fragile in nature. In the lymph node dissection material, 10 right pelvic and 8 left pelvic lymph nodes were detected. Macroscopic evaluation of the left kidney, which was operated due to atrophy, revealed a dilated pelvicalyceal system, thinned cortex, and a 0.3 cm diameter stone in the calyx.

Histopathological evaluation of the mass revealed mesenchymal differentiation forming the majority of the tumor (Figure 1, short arrows) with wide eosinophilic cytoplasm, vesicular nucleus, prominent nucleolus, locally spindle-shaped and locally multinucleated bizarre giant cells (Figure 2) which is separated from the high grade papillary carcinoma confined to a focal area (Figure 1, long arrow) by a sharp border. In the cells showing mesenchymal differentiation, diffuse immune reaction to vimentin (Figure 3), and focal immune reactions to pancytokeratin (Figure 4, short arrow), cytokeratin 7 (CK7), and CD31 were observed. In the area showing epithelial differentiation, diffuse reactions were observed to pancytokeratin (Figure 4, long arrow), and CK7 and focal reactions were observed to CK20 (Figure 5, arrow), and epithelial membrane antigen (EMA). No reaction was observed to smooth muscle actin (SMA), muscle-specific actin, and desmin in neither epithelial nor mesenchymal areas. No reaction was observed with HCG in bizarre multinucleated giant tumor cells. In the light of these findings, the case was diagnosed as "sarcomatoid carcinoma". No tumor was observed in neither of the ureteral surgical margins. The tumor was observed to cross the bladder wall and invade the prostate. Tumor metastases were

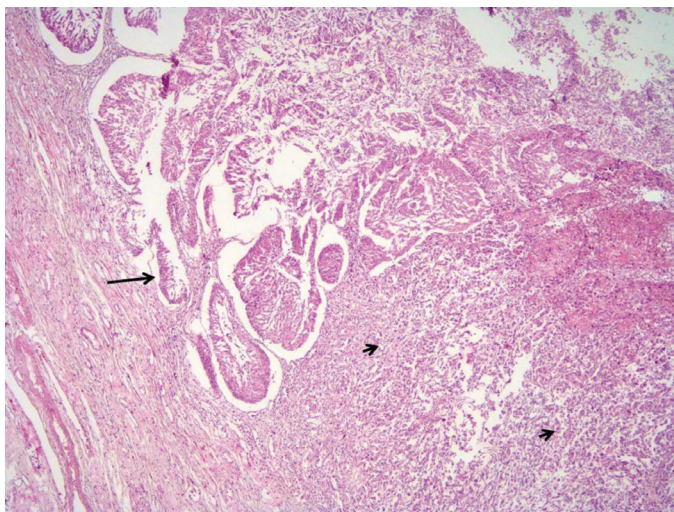


Figure 1. High grade papillary urothelial carcinoma (long arrow) and sharply demarcated mesenchymal differentiation areas (short arrows) (H & E x 40)

H & E: Hematoxylin and eosin

observed one at right pelvic lymph node and one at left pelvic lymph node. Microscopic evaluation of the left kidney revealed chronic pyelonephritis and atrophy; tumoral infiltration was not observed. No additional treatment should be given due to the worsening of his general condition, and the patient was died 2.5 months after the operation.

DISCUSSION

Sarcomatoid carcinoma, first described in 1935, develops in many organs and tissues such as the genitourinary system, respiratory system, gastrointestinal system, hepatobiliary system, pancreas, thyroid, skin, breast, spleen, and peritoneum (4). The clinical course of these tumors seen in different organs also differ.

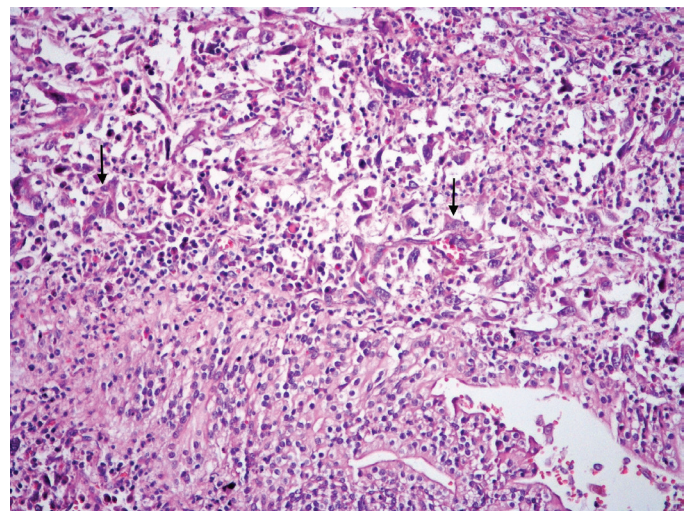


Figure 2. Multinucleated bizarre giant cells at areas showing mesenchymal differentiation (H&E x 100)

H & E: Hematoxylin and eosin

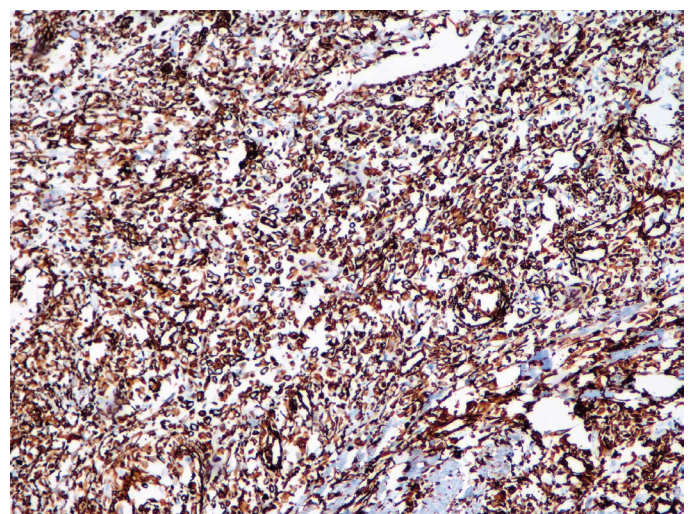


Figure 3. Diffuse immune reaction to vimentin in cells which demonstrate mesenchymal differentiation (IHK x 200)

IHK: Immunohistochemistry

A total of 835 cases, including 522 cases in the SEER database analysis between January 1960 and January 2010, and 313 cases in 13 studies between January 2010 and 2014, were reported (5). As a result of our search using the keywords “carcinosarcoma”, “sarcomatoid carcinoma”, and “bladder tumor” in Pubmed database, we determined 32 more cases between February 2014 and August 2017. Thus, we detected that 867 sarcomatoid bladder carcinomas were reported in the literature between January 1960 and August 2017 (1,5-24). The clinicopathological features of these cases are presented in Table 1.

In the World Health Organization 2016 classification, “sarcomatoid carcinoma” terminology is used for all biphasic

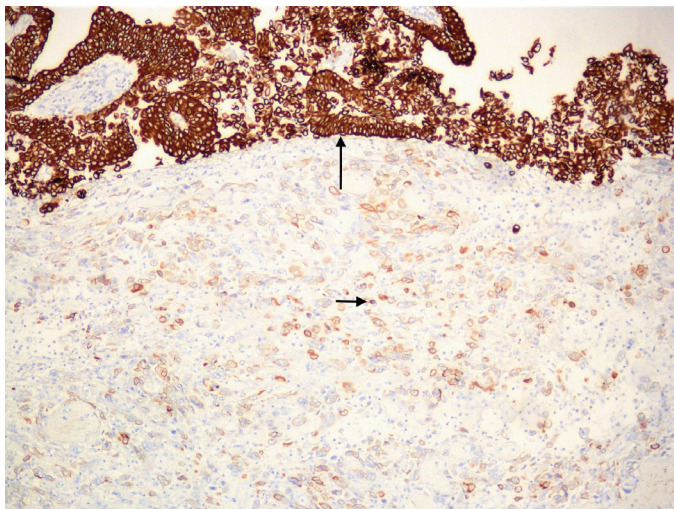


Figure 4. Diffuse strong positive reaction at areas with epithelial differentiation using pancytokeratin (long arrow) and focal immune reaction at areas with mesenchymal differentiation (IHK x 200)
IHK: Immunohistochemistry

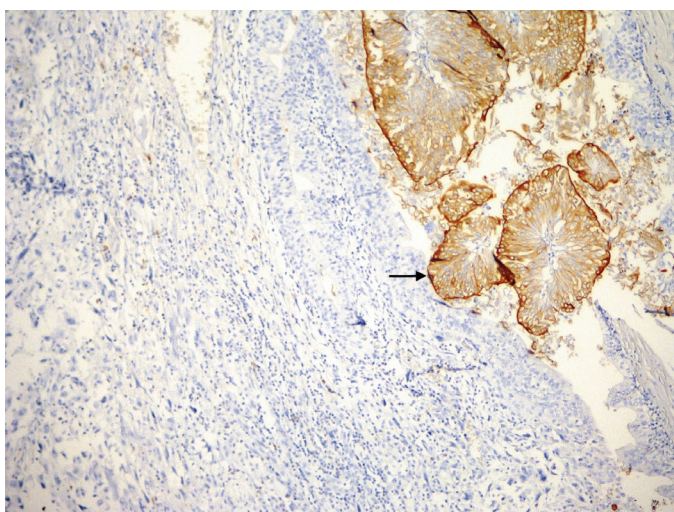


Figure 5. Focal immune reaction at epithelial differentiation areas with CK20 (IHK x 200)
CK: Cytokeratin, IHK: Immunohistochemistry

tumors of the urinary system containing epithelial and mesenchymal components. Two hypotheses have been proposed in the histogenesis of sarcomatoid carcinoma by molecular genetic studies. The first of these is the “dedifferentiation theory”, which is the altered differentiation of monoclonal tumors, and the second is the “collision theory” which involves the formation of urothelial and mesenchymal tumors synchronously. According to the dedifferentiation theory, the sarcomatous component of sarcomatoid carcinoma is due to the dedifferentiation of some of the urothelial cancer stem cells to the mesenchymal phenotype. Harmonious genetic differentiation in carcinomatous and sarcomatous components and expression of epithelial markers by both components support this hypothesis. The “collision theory” suggests that the carcinomatoid and sarcomatoid components develop separately from urothelial and mesenchymal stem cells. These stem cells cause the development of carcinoma and sarcoma in the same organ at the same time. Today, collision theory has lost its effect, and the dedifferentiation theory is widely accepted (25). Molecular genetic studies in recent years emphasize that the epithelial and mesenchymal components develop from a common monoclonal origin (5). In addition, Armstrong et al. (12) determined that p53 mutation in the epithelial and sarcomatoid component of the bladder sarcomatoid carcinoma is effective in the differentiation of both components in the early stages of tumor development.

Although the age of onset and clinical findings of sarcomatoid carcinoma of the bladder resemble conventional urothelial carcinoma, its prognosis is much worse. Therefore, it should be distinguished from other morphological variants (16). This tumor, which is generally seen in smoking men, has a female: male ratio of 1:3. Although smoking rate varies, a history of smoking was reported by 64% of the cases in Wang et al. (6) study, and in 88% of the cases in Başeskioglu et al. (17) study. In addition, a history of radiotherapy, diabetes mellitus, neurogenic bladder, bladder diverticulum, and cyclophosphamide use are among other risk factors (26,27). In our case, no smoking history and any other risk factors other than male gender were determined. Sarcomatoid carcinoma of the bladder has been reported between the ages of 10 and 96, with an average age of 66. Our case was 75 years old, which was the age range defined in the literature.

The most common symptom of admission in cases of sarcomatoid carcinoma is macroscopic hematuria; other symptoms are dysuria, nocturia, abdominal pain, and urinary tract infection (11,17,19). Our case also applied with macroscopic hematuria. Sarcomatoid carcinoma is usually large at the time of diagnosis,

and the average size is 6.2 (0.6-16) cm. The most common location is the lateral wall, fundus and trigon, and bladder floor (11,16). In our case, the tumor mass was 7.5x6.1x1.8 cm and was larger than the average of the literature. It had a wide distribution involving bladder floor, right and left walls, front and back walls, and trigon. Hemorrhage, necrosis, and cystic areas can be seen on the cross-sectional surface of these tumors (25). Although the epithelial component is composed of high-grade invasive urothelial carcinoma in most cases, it may also contain different types of carcinomas, such as squamous cell carcinoma, adenocarcinoma, or small cell carcinoma (28). The mesenchymal component is mostly composed of undifferentiated spindle or pleomorphic cells, rarely may include chondrosarcoma, osteosarcoma, rhabdomyosarcoma, liposarcoma, and angiosarcoma (3,25). In the Lopez-Beltran et al. (11) study, chondrosarcoma was reported to be 20%, leiomyosarcoma 20%, malignant fibrous histiocytoma 20%, osteosarcoma 13.3%, fibrosarcoma 6.7% and rhabdomyosarcoma 6.7% for the mesenchymal component. In our case, the mesenchymal component was spindle-shaped

in some locations, multinuclear with a giant cell appearance in other locations, and no heterologous element such as muscle, bone, or cartilage was observed. In such tumors, the epithelial component may react to epithelial markers such as pancytokeratin and EMA, while the mesenchymal component may show an immune reaction to the vimentin and epithelial markers as well as the reaction may depend on the heterologous element it contains (1). Since sarcomatoid component is very important in treatment and prognosis, it must be determined by immunohistochemical study. The immunohistochemical panel consisting of pancytokeratin, high molecular weight cytokeratin, p63, vimentin, SMA, and desmin has been shown to be useful in determining epithelial and sarcomatoid components (29). In our case, the results of immunohistochemistry were consistent with the literature. Malignant nonepithelial neoplasms should be considered in the differential diagnosis in small biopsies where sarcomatoid areas occupy a large portion. In this case, it may be necessary to apply a wide immunohistochemistry panel. SMA for inflammatory myofibroblastic tumor, SMA, and lemin

Table 1. Clinicopathological features of the cases

	Number of cases/diagnosis	Smoking history (%)	Hematuria (%)	Mean age (minimum-maximum)	Male/female ratio	Tumor size (cm) (minimum-maximum)	Number of metastatic lymph nodes
Wang et al. (6)	221/SC	U	U	75 (41-96)	2	U	15
Wright et al. (7)	135 / SC 166 / CS	U	U	U	1.6/SC 1.96/CS	U	23
Spiess et al. (8)	17/SC	U	U	69 (40-88)	1.8	U	U
Young et al. (9)	12/SC	U	75	71.5 (60-83)	1.4	U	U
Wang et al. (10)	14/SC	64	100	63 (45-93)	6	4.5 (0.6-8)	50
Lopez-Beltran et al. (11)	26/SC 15/CS	U	70/SC 77/CS	66.5 (41-91)	4.2/SC 2/CS	6.2/SC 7.8/CS	15/SC 20/CS
Armstrong et al. (12)	17/SC	U	U	64 (44-83)	16	U	20
Sung et al. (13)	30/SC	U	U	67.5	2	U	U
Monn et al. (14)	15/SC	U	U	62.9	1.5	U	U
Guo et al. (15)	87/SC	U	84	66 (18-89)	3.8	72% >3 cm	U
Ikegami et al. (16)	14/SC	U	U	76 (50-82)	1.8	3	U
Torenbeek et al. (1)	18/SC	U	94	72 (49-88)	2.6	4.5 (2-10)	44
Başeskioglu et al. (17)	14/SC	88	100	65 (41-86)	6	5.5 (3-16)	21
Jones and Young (18)	25/SC	U	U	72 (50-92)	1.3	6.8 (3-15)	U
Perret et al. (19)	8/SC	U	100	70 (50-85)	1.67	5 (2-10)	U
Wang et al. (20)	1/SC	U	100	10	Female	6	No
Bernardes Filho et al. (21)	1/SC	U	100	63	Male	10	U
Sanfrancesco et al. (22)	28/SC	U	U	70 (45-92)	17/11	U	10
Yasui et al. (23)	1/SC	U	100	47	Male	11	U
Lembo et al. (24)	1/SC	U	100	77	Male	13	U

U: Undefined, SC: Sarcomatoid carcinoma, CS: Carcinosarcoma

for leiomyosarcoma, CD34, and STAT6 for perivascular epitheloid cell tumor, CD31 and CD34 for solitary fibrous tumor, CD31 and CD34 for vascular tumors, are the main immunomarkers to be used in the differentiation of nonepithelial neoplasia (22,30,31).

Nodal and distant metastasis, which are determined at 10% in urothelial carcinoma is above 20% in sarcomatoid carcinoma. In the literature, tumor metastasis was detected in most of the cases with a diagnosis of sarcomatoid carcinoma in which lymph node was dissected, and tumor metastasis was detected in one left and one right pelvic lymph nodes in our case. This tumor has a worse prognosis than advanced stage urothelial carcinoma (7). There is no standard treatment for sarcomatoid carcinoma yet, as it is a rare variant, and no randomized controlled trials are available. Multidisciplinary treatment consisting of surgery, local radiotherapy, and chemotherapy is applied in locally advanced tumors. Although radical cystoprostatectomy is recommended in surgical treatment, Özkan et al. (28) performed partial cystectomy because their patients refused radical surgery, and they did not detect recurrence in their 24-month follow-up. In the 80-year-old metastatic sarcomatoid carcinoma case reported by Froehner et al. (32), gemcitabine and cisplatin were used as systemic chemotherapy and local and distant remission was achieved. Local recurrence and distant metastasis were not detected in the patient who was followed by Onal et al. (33) with adjuvant RT treatment after total cystectomy. The effect of radiotherapy alone has not been demonstrated in this tumor (11). Adjuvant radiotherapy indications have been reported as high grade tumors, extravesical extension, surgical margin positivity, lymph node metastasis, and lymphovascular invasion (34). Five-year disease-free survival is 20% (27). The most important predictive factors for long-term survival are surgical margins and metastasis. The prognosis is poor in cases with metastasis. In the study in which Lopez-Beltran et al. (11) examined 41 cases, the average survival was 10 months. According to the latest SEER data analysis, the most important predictive factor in survival was the pathological stage. In our case, a body scan was performed, and distant metastasis was not detected. Our case didn't take any treatment after the operation, her general condition was deteriorated, and she died after 2.5 months.

CONCLUSION

In conclusion, it is important to keep in mind the sarcomatoid carcinoma, which has a more aggressive course and shorter survival compared to urothelial carcinoma in order to determine

the correct diagnosis and the most appropriate treatment approach. In particular, taking multiple samples from large tumors is important to identify different components such as our patient, who initially appeared to have only high-grade urothelial carcinoma. The most important factor which determines survival is the pathological grade. Multidisciplinary treatment consisting of surgery, chemotherapy, and radiotherapy should be tailored by evaluating the stage of the disease and the general condition of the patient.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Two Cases; Extra-articular Synovial Chondromatosis of Flexor Compartments of the Wrist

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Abstract

Synovial chondromatosis is a benign synovial neoplasm. Its main characteristic is the formation of cartilaginous nodules in synovial joints, bursae and tendon sheath. It usually presents between the third and fifth decades. The most affected joints are knees, hips, elbow and shoulders; it usually affects only one joint. Patients usually complain of painless mass or swelling, and also reduced range of motion or joint blockage. We present two cases of extra-articular involvement of synovial chondromatosis in the flexor compartments of the wrist.

Keywords: Gelatin-like foreign bodies, tendon sheath, carpal tunnel, wrist tumors, synovial tumors

INTRODUCTION

Synovial chondromatosis is a rare neoplasm that is caused by metaplasia of the synovium into chondrocytes (1). Secondary calcification and ossification commonly occur. The etiology remains unclear and the most common site is in the large joints, predominantly the knee (40% of cases) followed by hip and shoulder, rarely affecting the wrist joint (2-4).

Traumatism and infections along with fibroblast growth factors have been implicated in the pathogenesis (5,6). The extra-articular form develops from tendon sheaths or articular membranes and it affects mainly the hand and wrist structures (7,8). These cases describe an unusual synovial chondromatosis involving the flexor compartments of the wrist, an extra-articular location.

CASE 1

Fifty nine years old male patient admitted to out-patient clinic with enlarging mass on volar side of his left wrist for 3 years. Patient was complaining about the numbness in the distribution of median nerve and local swelling without pain. Detailed history revealed that he was aware of the lump for 2 years, but severity

of the numbness became prominent for 4 months. Numbness and tingling sensation were varying in intensity and present at different times of the day. In physical examination, 15x5 cm lump at the level of flexor retinaculum was noted. Prominent hypoesthesia in the distribution of median nerve was stated and minimal pain was present with provoked hyperextension of the wrist. Evaluation of the wrist range of motion conducted significant multi-planar restriction.

No specific findings were present in conventional anteroposterior (AP) and lateral radiography except minor soft tissue swelling (Figure 1). Magnetic resonance imaging (MRI) evaluation stated that 12x4 cm multiple fusiform shaped nodules were surrounding the flexor tendons and filling the carpal tunnel, nodules were hyperintense in T1 weighted images and isointense in T2 weighted images (Figure 2).

The patient underwent resection surgery by the light of clinical evaluation. Volar approach to the carpal tunnel was preferred. Following the deep dissection, surrounding sac shaped mass is removed and intraoperative puncture of the sac exposed many chondroid nodules. Histopathologic examination revealed chondroid nodules covered with synovial and fibrous cells



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and hyaline cartilage tissue related with synovial cells (Figure 3). Diagnosis was confirmed as synovial chondromatosis. No recurrence was reported following 16 months post-operatively.

CASE 2

Fifty five years old female patient admitted to out-patient clinic with enlarging mass on volar side of his left wrist for 2 years. Multiple lobulated mass at the volar side of the wrist beginning from the flexor retinaculum and reaching 8 cm proximally was palpated in physical examination. No specific findings were present in conventional AP and lateral radiography except minor soft tissue swelling. MRI evaluation stated that 9x4 cm, multiple fusiform shaped nodules were surrounding the flexor tendons and filling the carpal tunnel, nodules were hyperintense in T1 weighted images and isointense in T2 weighted images.

Identical surgical procedure was applied for the patient. Following the deep dissection, surrounding sac shaped mass is removed and intraoperative puncture of the sac exposed many



Figure 1. Conventional AP and lateral radiography; there is no specific finding except minor soft tissue swelling
AP: Anteroposterior

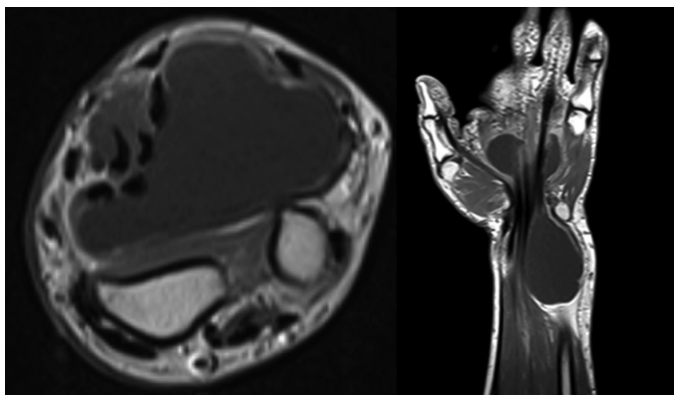


Figure 2. MRI images stated that 12x4 cm multiple fusiform shaped nodules were surrounding the flexor tendons and filling the carpal tunnel, hyperintense in T1 weighted isointense in T2 weighted images
MRI: Magnetic resonance imaging

chondroid nodules. Histopathologic examination revealed chondroid nodules covered with synovial and fibrous cells and hyaline cartilage tissue related with synovial cells. Diagnosis was confirmed as synovial chondromatosis. No recurrence was reported following 12 months post-operatively.

DISCUSSION

Extra-articular synovial chondromatosis is a benign but locally aggressive disease. The most common symptom is a slowly enlarging soft tissue mass. Chief complaint of the both patient was progressively enlarging mass without pain. There is no age or gender predilection for the extra-articular synovial chondromatosis (9). In a literature review by Vinaixa et al. (10) evaluated 30 patients with synovial chondromatosis and there were 12 male, 11 female and 6 patients with missing data. Vinaixa also stated that 5 out of 30 (17%) patients had recurrence in 6 to 108 months follow-up. Moreover, even there was no vascular pathology observed 4 out of 30 patients had neurologic complications involving median and ulnar nerve with varying severity. In our cases there is no vascular pathology observed, only in case 1 there is median nerve neurologic symptoms observed.

We introduced 2 new cases to known literature. We had 1 male and 1 female patient with synovial chondromatosis located in carpal tunnel. Even there is no recurrence observed in our cases, expanded follow-up times required to place valid statement about recurrence rates. In our study, we also had no vascular pathology encountered, but first case had prominent median nerve compression signs. Malignant transformation of synovial chondromatosis into chondrosarcoma is an extremely rare event; Vinaixa et al. (10) did not identify any malignant transformation in their review. Davis et al. (11) identified three patients with malignant transformation, from 53 patients with primary synovial chondromatosis and none of these involved

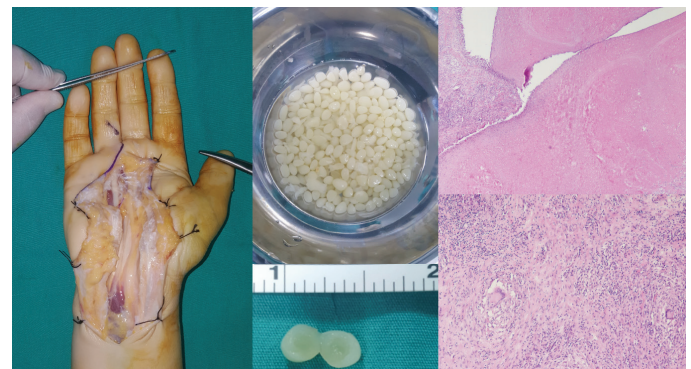


Figure 3. Histopathologic images show that chondroid nodules covered with synovial and fibrous cells and hyaline cartilage tissue related with synovial cells

the wrist joint. It has to keep in mind that, patients have to be under surveillance for malign transformation for longer period of time even the risk is relatively low.

Clinical diagnosis is not simple because tests often do not give any clear evidence. The most common symptoms are swelling with pain, deformities and reduced joint function caused by compression of the structures (8). Sometimes the clinical picture is silent since there may be no pain or functional limitation but only a lot of swelling without any history of trauma as were the two cases for our patient. After the clinical diagnosis, we proceeded to radiological evaluation. Routine X-ray examination is usually adequate for the diagnosis. X-ray examination shows that soft tissue mass with multiple small calcified or ossified densities (12). But the lack of ossification or calcification of the nodules at the beginning of the disease X-ray did not give anything to diagnosis of the synovial chondromatosis as our cases. If the X-ray is inadequate for diagnosis, MRI will be useful for the diagnosis and clarify the extension of the lesions (12). Conventional radiography provided insufficient data for diagnosis for both cases. Due to the hiperintense appearance in T1 weighted images and isointense presentation in T2 weighted images nodules were not clearly identified. However, these findings in MRI are highly characteristic for synovial chondromatosis (13).

The disease follows three phases, which was described by Milgram (14). In the first phase only active intra-synovial disease exists without loose bodies, in the second stage there are active synovial proliferation and loose bodies are present, and in the third and final stage multiple loose bodies are present without intrasynovial disease. Both of our patients had multiple chondroid bodies and synovial proliferation therefore classified as stage 3 synovial chondromatosis.

CONCLUSION

In conclusion, we would like to point out those two giant synovial chondromatosis cases localized in flexor compartment. Even typical presentation of the pathology is mostly involved in major joints; extraarticular presentation is also possible and should be considered in differential diagnosis. We recommend long-term follow up for probable recurrence.

Ethics

Informed Consent: Consent was obtained from patients for this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Giant Cell Arteritis

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Abstract

A 76-year-old lady presented to emergency department for left eye sudden visual loss, and funduscopy found cherry-red spot over the central macula with attenuated retinal vessels. Central retinal artery occlusion (CRAO) was diagnosed. She did not complain of new onset headache, but mild tenderness on palpation over left temporal area with vaguely weak pulsation detected. After the acute management of CRAO pharmacologically, rebreathing into paper bag, and ocular massage; patient underwent hyperbaric oxygen therapy hoping to salvage the ischemic retina while waiting for the erythrocyte sedimentation rate result. Result was >100 mm/hr, and high dose oral steroid was started immediately. Superficial temporal artery biopsy (TAB), performed 2 days after steroid treatment, was diagnostic of giant cell arteritis (GCA). Positron emission tomography and computerized tomography scan revealed vasculitis over thoracic aorta, left common carotid and subclavian artery. Ocular imaging of CRAO, histology of GCA on TAB are discussed with the interesting images.

Keywords: Giant cell arteritis, central retinal artery occlusion, fundus fluorescein angiography, temporal artery biopsy

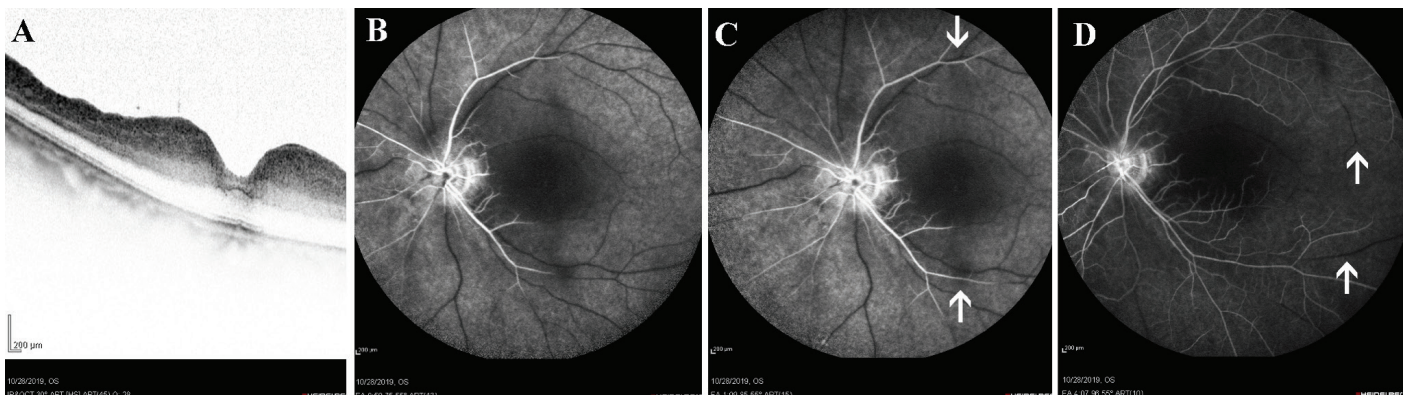


Figure 1. Fundus fluorescein angiography (FFA) is an investigation of the retinal vasculature with the injection of intravenous fluorescein dye (1), which appears as white colour on photography, whereas the non-perfused vasculature appears as black colour. Normal retinal arteries filling time is 10-13 seconds, while complete filling of veins at 16-20 seconds.

In our case, cross sectional view over the left eye foveal retina by optical coherence tomography (Figure 1A) showed inner retinal thickening from ischemia to almost double of normal. FFA photos taken at 10-20 seconds after the injection of dye were completely blackout. At around 1 minute (Figure 1B), FFA showed generalized delay and incomplete arterial filling of the retinal arteries, compatible with central retinal artery occlusion (CRAO). Figure 1C taken 10 seconds later showed minimal advancement of arterial filling only compared to filling position in Figure 1B (indicated by white arrows). Beyond 4 minutes (Figure 1D), not even all retinal veins were filled (indicated by white arrows) by the fluorescein indicating persistence absence of blood flow.

CRAO is a clinical diagnosis by funduscopy for the presence of cherry-red spot over the central macula, generalized pale retina (edema caused by ischemia) with attenuated retinal vessels. Acute management of CRAO are pharmacologically to lower the intraocular pressure, rebreathing into paper bag and ocular massage (2). Underlying etiology for CRAO needs to be dealt with, such as giant cell arteritis (GCA) requires high dose steroid treatment (3). Hyperbaric oxygen therapy, if indicated and available, may help re-perfuse the ischemic retina by choroidal circulations (4).



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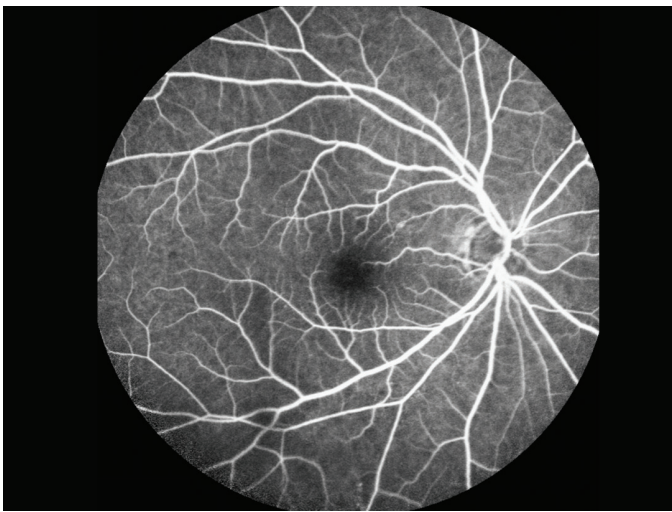


Figure 2. This FFA photo of the normal right eye taken at 48 seconds after the injection of dye (Figure 2) showed well perfused retina with filling of dye in both retinal arteries and veins.

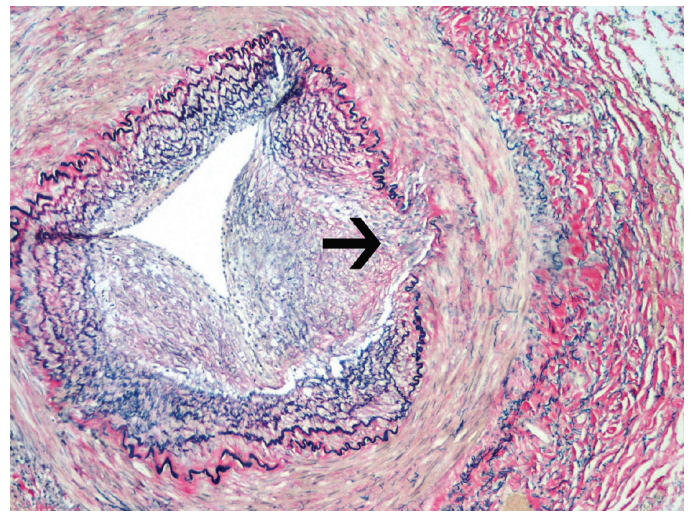


Figure 4. Elastic van Gieson stain is useful for highlighting the elastic fibers (8). In another level of cut over the TAB specimen (Figure 4), it demonstrated the disruption of internal elastic lamina at the site filled with inflammatory infiltrate (indicated by black arrow).

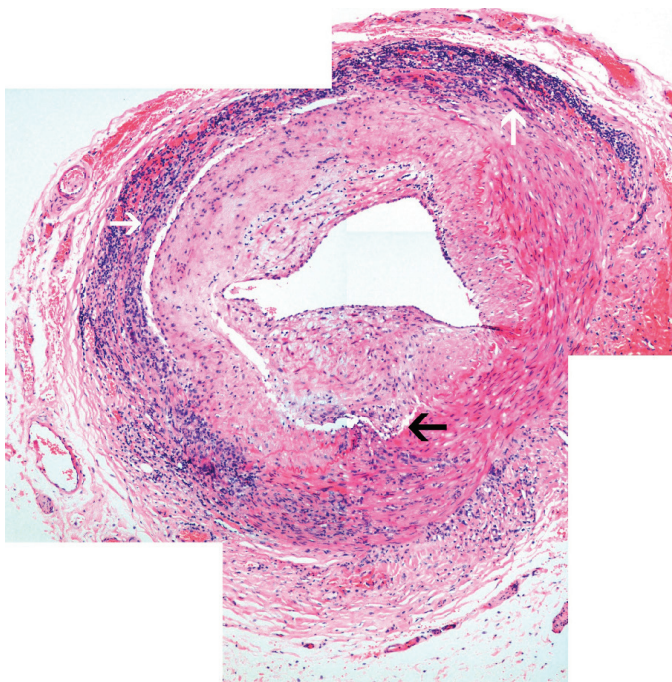


Figure 3. Superficial temporal artery biopsy (TAB) is one of the diagnostic criteria for GCA (5). This combined histology photo (Figure 3) from 3 high magnification (40x) films illustrated the cross sectional view of the temporal artery stained with haematoxylin and eosin. It showed narrowing of vascular lumen from concentric intimal hyperplasia (6). There was prominent transmural inflammatory infiltrate (highlighted as blue colour by the stain) accompanied by multinucleated giant cells (indicated by white arrows) at the level of internal elastic lamina, and loss thus fragmented internal elastic lamina (indicated by black arrow). Giving the name of GCA, giant cell is formed by fusion of epitheloid cells, activated macrophages, which the nuclei form semicircle in horseshoe configuration away from the eosinophilic centre of the giant cell. However, absence of giant cell on TAB specimen does not exclude GCA, as skip lesion is common in this type of large vessel vasculitis (7).

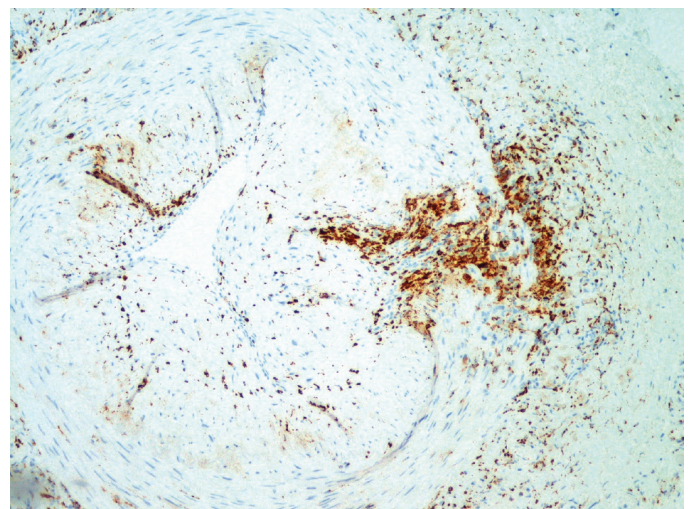


Figure 5. Immunohistochemistry staining over the TAB specimen for cluster of differentiation-68 (Figure 5) highlights the dense distribution of macrophages (brown colour) over the disruption of internal elastic lamina.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Concept: S.C.L.A., Design: S.C.L.A., Data Collection or Processing: S.C.L.A., Analysis or Interpretation: S.C.L.A., Literature Search: S.C.L.A., S.T.C.K., Writing: S.C.L.A.

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

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

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