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Duration of Labor with Meperidine Versus Placebo in Singleton Term Pregnancies: A Randomized Placebo Controlled Study

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Abstract

Objective: Meperidine, a synthetic opioid analgesic, is used empirically in many birth centers due to its effect on the duration of labor as well as pain relief during labor. In this study, we examine the effect of meperidine administration on the duration of labor.

Methods: This study was designed as a prospective randomized placebo-controlled study; 250 patients were randomized into two groups where the study group received 0.5 mL-25 mg i.v. meperidine and the control group received 0.5 mL i.v. saline solution, all at the start of the active phase. The start of the active phase of labor was defined as 4 cm cervical dilatation and 60%-70% cervical effacement. The primary outcome was determined as the duration of the active phase (DAP). This study is registered on ClinicalTrials.gov (identifier: NCT01555671).

Results: Women randomized to the meperidine group had a shorter total duration of labor (TDL) and shorter duration of the DAP compared to the control group, both in the total patient population women (mean ± standard deviation (SD): 273±129 min vs. 331±177 min, p=0.033; 249±122 min vs. 304±167 min, p=0.029, respectively) and in primiparous (mean ± SD: 372±134 min vs. 400±179 min, p=0.026; 296±126 min vs. 363±170 min, p=0.024, respectively). No statistically significant difference was found between the total patient population and primiparous group in terms of the second stage of labor (DSS) (p=0.930, p=0.229; respectively). Multiparous women in meperidine and control groups, did not show a statistically significant difference in terms of the TDL, DAP and the DSS (p=0.170, p=0.157, p=0.498; respectively). No statistically significant difference was found between the two study groups in terms of age (p=0.126), parity (p=0.427), body mass index (p=0.163), cesarean rates (p=0.511) and mean gestational weeks (p=0.845).

Conclusion: Our findings revealed that meperidine administration was associated with a shorter duration of active phase of labor in primiparous women.

Keywords: Active phase, apgar, duration labor, labor analgesia, meperidine, pethidin

INTRODUCTION

The onset of labor is characterized by regular, painful uterine contractions that increase in frequency and intensity resulting in progressive cervical dilatation and effacement. Historically, the stages of labor are based on the observations first made by Friedman and Kroll (1). Because of these observations, the first stage of the labor process was defined as the completion of cervical dilatation, and the second stage as the descent and expulsion of the fetus. With the demonstration of the labor curves for the progression of normal birth and the definition of stages of labor, Friedman's work still constitutes the benchmark for the diagnosis of prolonged labor in today's obstetric practice (2). Prolongation in the first and second stages of labor may lead to increased cesarean rates, operative delivery, and low Apgar scores (3). Shortening of labor duration or preventing labor prolongation, can reduce these adverse outcomes, besides the

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advantage of shorter exposure of the mothers to labor stress and pain. Although labor augmentation is used routinely in some crowded labor wards to avoid complications due to labor prolongation, this practice is not evidence-based (4).

Many non-pharmacological and pharmacological methods have been used for augmentation of labor. These relationships have been tried to be explained by more than one mechanism (5). There is some evidence that the administration of meperidine (another common name is pethidine) (6,7) , which is a method for augmentation, may affect the duration of labor besides its analgesic effect, although the literature is contradictory (8,9). There are some studies showing that meperidine increases uterine contractions (6). Based on its association with uterine contractility (direct or via pain relief) and changes in cervical proteases, meperidine is considered amongst the methods of accelerating labor by stimulating uterine contractions and facilitating cervical dilation (10,11). Another important fact in the widespread use of meperidine is the scarcity of epidural analgesia in public hospitals in Turkey; therefore, many clinicians frequently use meperidine to reduce pain during labor or to accelerate duration of labor. However, few studies have found no association between the drug and uterine contractions and cervical changes (12,13).

Furthermore, there are very-limited numbers of placebo-controlled studies and inconsistent data regarding the efficacy of meperidine on shortening of the duration of labor. This prospective randomized placebo-controlled study was therefore designed to evaluate the impact of meperidine administration on the duration of active labor in relation to parity and neonatal outcomes in singleton term pregnancies.

METHODS

This prospective, randomized, double-blind, placebo-controlled study included 250 consecutive women who gave birth at University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Resarch Hospital, Istanbul-Turkey between January 2012 and May 2012. The hospital is a tertiary referral center with an average of greater than 15,000 deliveries per year. The sample size was calculated using Number Cruncher Statistical System/PASS 2007, based on the active phase labor duration of minimal critical importance (30 min) (14) and mean [standard deviation (SD)] 296.04 min (170.02) values obtained from first 20 control subjects revealing that for statistical power of 80% and significance (α) of 0.05, at least 200 patients (100 patients in each group) should be included in the study.

Nulliparous or multiparous women aged 18-40 years with a singleton pregnancy of 37-42 weeks that were in active labor, with 4 cm cervical dilatation, 60%-70% effacement and fetal head engagement or Bishop score 6 were included in the study. The presence of maternal hypertension, comorbid chronic diseases (i.e. diabetes, thyroid disease), fetal developmental problems, abnormal external fetal cardiotocography findings (i.e. uterus hyperactivity, lack of continuous reactivity), cephalo-pelvic disproportion, vaginal bleeding, past history of uterine surgery or preterm delivery, early membrane rupture, and obstetric complications such as preeclampsia were the exclusion criteria of the study.

In the meperidine group, meperidine 25 mg IV bolus injection (0.5 mL) was administered when the cervical dilatation was 6 cm with 60%-70% effacement. The same amount (0.5 mL) of saline solution was given IV to the subjects in the control group. Enrolled women were randomly assigned to two groups as the study (meperidine group) and placebo group (control group). Randomization was performed according to a computer-generated list of numbers which were recorded in sealed envelopes, containing identical syringes containing either 0.5 mL of meperidine 25 mg or 0.5-mL saline, prepared by a nurse who was not involved in the study. Envelopes were chosen randomly by the principal investigator randomly, both the patient and investigators were blinded for the intervention. All participants underwent a general physical examination and an obstetric examination. The vaginal was examined every hour to assess the progress of labor. In our delivery unit, labor augmentation is performed with oxytocin in accordance with the routine protocol of our hospital. Starting from 6 mU/min, oxytocin is increased by 6 mU/min every 20 min to achieve a regular contraction pattern to a maximum infusion rate of 42 mU/min. Uterine activity of 200-250 Montevideo units is considered adequate. Routine amniotomy was performed in all patients with cervical dilatation of 6 cm or more if spontaneous rupture of membranes had not occurred.

All patients were followed up with external cardiotocography. The delivery procedure is routinely performed according to our hospital's delivery protocol. During delivery, episiotomy is performed by the doctor in line with his or her clinical approach when deemed necessary. The duration of the active phase of labor was recorded as the time (min) from a cervical dilatation of 4 cm until the cervical dilatation was completed. The duration of the second phase of labor was recorded as the time (min) from full cervical dilatation to the delivery of the fetus. In our hospital, cesarean delivery indication and decision is in the responsibility of the obstetrician who is in charge of the labor ward, the same protocol was followed throughout the study. Patients who delivered by cesarean were excluded from the study.

The primary outcome measures were defined as the time from 4 cm with more than 60% effacement to full cervical dilatation duration of the active phase (DAP). Secondary outcome measures were defined as duration of second stage of labor (DSS), (total labor duration: DAP + DSS), need for episiotomy, birth weight, 1-min and 5-min Apgar scores, and presence of meconium aspiration. Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Yeditepe University Faculty of Medicine Clinical Research Ethics Committee (date of approval: 02/11/2011; reference number/protocol no: 2011/121) (ClinicalTrials.gov Identifier: NCT01555671).

Statistical Analysis

Data analyses were made using statistical software SPSS (version 11.5, IBM, New York, USA). Fischer's Exact test and Pearson χ^2 tests were used for the comparison of categorical data. Numerical variables were analyzed using the Student's t-test for parametric variables or the non-parametric Mann-Whitney U test when data were not normally distributed. Data were expressed as "mean ± SD," "median [minimum (min) - maximum (max)]"and "n (%)", where appropriate. P<0.05 was considered statistically significant.

RESULTS

Demographic Characteristics

A total of 449 consecutive singleton pregnancies admitted to the labor ward with the complaint of labor pain and the diagnosis of onset of labor were included in the study. One hundred ninety nine patients who were ineligible for the study were excluded and 250 patients, 125 laboring women in the study group and 125 laboring women in the control group, were included in the study (Figure 1). The mean age was 25.2±5.1 years in the meperidine group, 26±4.8 years in the placebo group, and the differences were not significant (p=0.126). In terms of gestational weeks, median gestational week was 39 weeks 2 days (min-max: 37-42) in the control group, and 39 weeks (min-max: 37-42) in the meperidine group. No statistically significant difference was found between the groups (p=0.845). Twenty (16%) patients in the study group and 25 (25%) patients in the control group had to deliver by cesarean section. Although cesarean section rates were higher in the control group, the difference was not statistically significant (p=0.511). Likewise, there was no difference between the two groups in terms of body mass index (mean ± SD; study group: 28.85±4.52, control group: 27.95±3.43, p=0.163). When

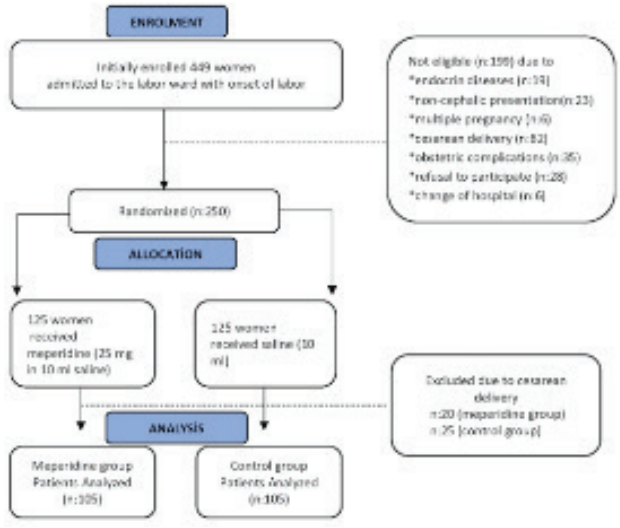

Figure 1. Consort statement flow diagram

the groups were subdivided in terms of parity (primiparous and multiparous), the mean number of patients in the groups was similar. No significant difference was observed in terms of subgroup numbers between meperidine and control groups and in terms of subgroup demographic parameters between multiparous and primiparous women in the overall study population. The demographic and obstetric characteristics of the participants are shown in Table 1.

Labor Characteristics and Neonatal Outcomes

TDL and DAP were found to be statistically significantly shorter in the meperidine group compared to the control group, both in primiparous (mean ± SD: 372±134 min vs. 400±179 min, p=0.026; 296±126 min vs. 363±170 min, p=0.024) and in the total patient population (mean ± SD: 273±129 min vs. 331±177 min, p=0.033; 249±122 min vs. 304±167 min, p=0.029). In contrast, for the DSS, no statistically significant difference in mean duration time was observed between meperidine and control groups in the total patient population, multiparous and primiparous women groups (mean ± SD: 24±15 min vs. 27±22 min, p=0.930; 15±8 min vs. 16±15 min, p=0.498; 30±15 min vs. 36±23 min, p=0.229, respectively). Although the meperidine group had shorter durations in terms of TDL and DAP in the multiparous patient population, no statistically significant difference was found between the groups (mean ± SD; 197±72 min vs. 258±144 min, p=0.170; 181±69 min vs. 241±139 min, p=0.157, respectively). No significant difference was noted between meperidine and control groups regarding total population and subgroups as primiparous and multiparous in terms of need for episiotomy, birth weight, 1-min and 5-min Apgar scores and presence of meconium aspiration (Table 2).

Table 1. Demographic characteristics of patients in the placebo and study groups by parity										
Control (n=100)		Total (n=205)			Multiparous women (n=91)			Primiparous women (n=114)		
		Meperidine (n=105)	p value	Control (n=48)	Meperidine (n=43)	p value	Control (n=52)	Meperidine (n=62)	p value	
Maternal characteristics										
Age (year)	Mean ± SD	26.03± 4.8	25.21±5.17	0.126[1]	28.08±4.63	28.70±4.70	0.593[1]	24.13±4.15	23.1±3.98	0.533[1]
BMI (kg/m^2), mean (min-max)		28.85 (19.47-47.23)	27.95 (14.5-40.16)	0.163[1]	29.88 (22.04-47.3)	28.11 (14.5-40.16)	0.073[1]	27.88 (19.47-37.32)	27.83 (20.2-34.45)	0.928[1]
Parity; mean ± SD		0.74±0.95	0.66±0.93	0.427[1]	1.54±0.80	1.60±0.76	0.550[1]			
Cesarean rates		25/125 (20%)	20/125 (16%)	0.511[1]	12/48	9/43	0.665[1]	13/52	11/62	0.767[1]
Gestational week, mean ± SD, mean (min-max)		39.3±1.51	39.3±1.29	0.845[1]	39.6 (37-41.6)	39.40 (37-41.5)	0.344[1]	39.0 (37.0-41.2)	39.0 (37.0-41.5)	0.421[1]
Parite	Primipar	52	62	0.310[2]	-	-	-	-	-	-
	Multipart	48	43							

[1]Mann-Whitney U test, p<0.05 were considered statistically significant, [2]Pearson χ^2 test. BMI: Body-mass index, SD: Standard deviation, min: Minimum, max: Maximum

Table 2. Labor characteristics and neonatal outcomes in study groups with respect to parity										
		Total (n=205)			Multiparous women (n=91)			Primiparous women (n=114)		
		Control (n=100)	Meperidine (n=105)	p value	Control (n=48)	Meperidine (n=43)	p value	Control (n=52)	Meperidine (n=62)	p value
Labor characteristics										
Duration of labor (min), mean ± SD										
Active phase		304±167	249±122	**0.029[1]**	241±139	181±69	0.157[1]	363±170	296±129	**0.024[1]**
Second stage		27±22	24±15	0.930[1]	16±15	15±8	0.498[1]	36±23	30±15	0.229[1]
Total		331±177	273±129	**0.033[1]**	258±144	197±72	0.170[1]	400±179	372±134	**0.026[1]**
Need for episiotomy, n (%)	No	25 (27.0)	28 (28.6)	0.785[3]	25 (52.1)	28 (65.1)	0.296[3]	0 (0.0)	2 (3.2)	0.499[3]
	Yes	75 (73.0)	77 (71.4)		23 (47.9)	15 (34.9)		52 (100.0)	60 (96.8)	
Neonatal outcomes										
Birth weight (g)	Mean ± SD	3270±480	3210±397	0.330[2]	3405±485	3378±398	0.450[1]	3217±408	3204±316	0.603[1]
	Median (min-max)	3295 (2050-4400)	3200 (2250-4400)		(2050-4400)	(2790-4400)		(2360-3871)	(2223-3860)	
Apgar score										
1 min	Mean ± SD	7.56±0.69	7.81±0.59	0.512[1]	7.66±0.64	7.84±0.5	0.537[1]	7.52±0.7	7.76±0.6	0.145[1]
	Median (min-max)	8.0 (6.0-9.0)	8.0 (6.0-9.0)		8.0 (6.0-9.0)	8.0 (7.0-9.0)		8.0 (6.0-9.0)	8.0 (6.0-9.0)	
5 min*	Mean ± SD	9.08±0.44	9.12±(0.43)	0.550[1]	9.0±(0.37)	9.1±(0.34)	0.640[1]	9.1±0.5	9.2±0.5	0.317[1]
	Median (min-max)	9.0 (7.0-10.0)	9.0 (8.0-10.0)		9.0 (8.0-10.0)	9.0 (8.0-10.0)		9.0 (7.0-10.0)	9.0 (8.0-10.0)	
Meconium aspiration, n (%)	No	81 (80.8)	84 (80.0)	0.884[3]	35 (75.0)	35 (81.4)	0.592[3]	45 (86.5)	52 (83.9)	0.422[3]
	Yes	19 (19.2)	21 (20.0)		12 (25.0)	8 (18.6)		7 (13.5)	10 (16.1)	

[1]Mann-Whitney U test, [2]Student's t-test, [3]Pearson χ^2 test, [4]Fisher's Exact test, where appropriate. P<0.05 was considered statistically significant. Bold written numbers: Statistically significant, *All infants' Apgar score was 7-10. SD: Standard deviation

DISCUSSION

In this study, we tested the hypothesis that meperidine administration shortened labor time in nulliparous women who had labor augmentation, and we found that in primiparous labor duration was shorter with meperidine administration compared to placebo administration. Sosa et al. (9) conducted a randomized controlled study to determine whether meperidine administration reduced the duration of labor in women diagnosed with dystocia in the first stage of labor; however, they

could not find a statistically significant difference between the 100 mg meperidine i.v. and placebo groups in terms of labor duration. Furthermore, El-Refaie et al. (15) also conducted a similar randomized controlled study with 50 mg meperidine i.v. in pregnant women diagnosed with dystocia, but they could not show a statistically significant decrease in labor duration with the use of meperidine. Both studies are inconsistent with our findings. These different results regarding the use of meperidine on the progression of labor, may be a consequence of disparity between the administration of meperidine in patients with labor dystocia and in patients who undergo routine augmentation during a normally progressing labor. Another study from Turkey, conducted with a patient population of 53 primiparous women, revealed that administration of meperidine (50 mg, slow i.v. infusion) at 4-6 cm cervical dilation significantly shortened the total duration of labor by 38% (119.8 min vs. 192.2 min for placebo) and the first stage of labor by 41% (103 min vs. 173 min for placebo) with no difference between meperidine and placebo in terms of duration of the second stage of labor (8). In the same study, no statistically significant difference was found between meperidine administration and placebo in the second stage of labor. These findings were similar to the findings in our study. We also consider that these similar results may be evaluated due to genetic similarities.

The progression of labor is considered faster in multiparous women than in primiparas, as it enables an earlier onset of stronger uterine contractions, associated with the higher sensitivity of the uterus to endogenous and exogenous oxytocin (16). Accordingly, there is a significant negative correlation between parity and duration of both active and second stages of labor in multiparous women in studies (17,18). In this context, in our study, primiparous women who received meperidine had a statistically significant shorter duration of active labor than primiparous women who received placebo, in contrast, the same effect was not observed in multiparous women. The lack of effect in multiparous women can be explained by the fact that the effect of parity on the duration of labor may mask the effect of meperidine.

Maternal safety remains a concern with any opioid-based analgesic technique used during labor. Meperidine has been associated with an adverse effect on neonatal outcome, including low Apgar scores and respiratory depression in neonates (19,20). However, a few previous studies (21,22) suggest that the risk of adverse neonatal outcome is related to 1) the dose of meperidine and 2) the time between meperidine administration and the delivery of the baby. Although studies show inconsistent results, 50 mg meperidine applications can be considered an upper limit (8,9,23). Therefore, given that fetal meperidine exposure is maximum 2-3 hours after maternal administration, the optimal time for delivery may be considered to be within the first hour or after the third hour of the dose of meperidine (23). However, it may be proper to be skeptical about this issue.

Generally, no significant difference was observed in terms of Apgar scores between the control and meperidine groups in our study. Sosa et al. (9) showed that lower Apgar scores and more neonatal intensive care needs were required in the meperidine group. This difference may be because the patient population was selected from patients with labor dystocia or those who needed active management in the second stage of labor and the dose of meperidine administered was higher. In this regard, 25 mg i.v. meperidine administration may be safe. More studies are needed on neonatal effects.

Study Limitations

It must be admitted that some confounding factors were not noticed at first due to the study. In particular, determining the onset of the active phase of labor and subjective measurement of cervical dilatation are among these factors. In this respect, studies using more objective measurement methods and strict criteria should be conducted. Another limitation of our study was that the acid-base status of the arterial and venous umbilical cord blood samples at birth was not determined in our study. The fact that maternal side effects (nausea, vomiting, dizzinesss, cooperation disorder, etc.) were not evaluated in the study and control groups may be another weakness of our study. Additionally, the follow-up of the newborns in the first days after delivery could not be evaluated in our study due to the working conditions of the hospital. Besides, it would be appropriate to evaluate maternal pain in each group using the post-intervention visual analog score test.

Our study is the first randomized-controlled study that we know of, examining the effects of meperidine on labor duration during normally progressing labor without additional conditions such as labor dystocia. It is also the first study that used a lower dose (25 mg) of meperidine than other studies, demonstrating that it shortens the duration of labor in primiparous pregnant women.

CONCLUSION

In conclusion, our findings revealed that meperidine administration was associated with a shorter duration of active phase of labor in primiparous women. No significant impact on and no deterioration in Apgar scores with meperidine administration was observed in both primiparous and

multiparous women. There is a need for further larger scale randomized clinical studies addressing the impact of meperidine on duration of labor and neonatal outcomes among primiparous and multiparous women by different doses at various stages of cervical dilatation with a thorough and comprehensive neonatal assessment.

Ethics

Ethics Committee Approval: Yeditepe University Faculty of Medicine Clinical Research Ethics Committee (date of approval: 02/11/2011; reference number/protocol no: 2011/121).

Informed Consent: Informed consent forms were signed by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: O.Ş., Design: O.Ş., Data Collection or Processing: O.Ş., N.Ç., Analysis, or Interpretation: O.Ş., G.Y., S.G., V.M., N.Ç., A.İ.T., Literature Search: O.Ş., G.Y., Writing: O.Ş.

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