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Original article

The Effect of Pethidine Analgesia on Labor Duration and Maternal-Fetal Outcomes

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Abstract.

Background and Aim: Opioid analgesics had been used from time to time for treating labor pain. However, their use have been concerning. The aim of this study is to evaluate the effect of pethidine on duration of active phase of labor, labor pain and maternal-neonatal outcomes. *Methods:* In the present case-control study, the study group received a 50 mg pethidine intramuscular injection upon the start of active phase of labor, and the control group consisted of patients who receive placebo injeciton. In both groups, vital signs were measured before, and at 0, 5, 15, 30, 45 and 60 minutes after the injection. Pain intensity was evaluated with Visual Analogue Scale (VAS) prior to, and 1 hour and 2 hours after injection. Data regarding labor phase durations, maternal side effects, newborn APGAR scores and fetal respiratory problems were recorded. *Results:* 102 patients in Pethidine group and 92 patients in control group, were included into the study. Labor pain VAS-scores were significantly lower in the study group ($p<0.001$). Moreover, active phase of labor duration was significantly shorter in the study group ($p<0.001$). Maternal pulse significantly decreased, and maternal nausea-vomiting was frequent in the study groups. However, the groups were similar in terms of other side effects and neonatal outcomes. *Conclusions:* Pethidine significantly reduces active phase of labor duration, has a favorable analgesic effect in treating labor pain and is not associated with serious maternal or neonatal complications. It is therefore considered an acceptable agent for use during active phase of labor. (www.actabiomedica.it)

Keywords : Analgesia, Active Phase, Pain, Pethidine, Labor

Introduction

One of the most important objectives of maternal care during labor is to provide efficient analgesia (1). Satisfactory analgesia improves the labor process (2,3). A major reason for the preference of cesarean section delivery is due to fear of pain during labor (4). Successful management of the active phase of labor is also associated with a decrease in cesarean delivery rates and maternal-fetal complications (1).

It is well known that pain during the 1st stage of labor evokes a general neuroendocrine stress response, and is associated with significant changes in oxygen consumption, acid-base balance, cardiopulmonary functions, and irregular uterine contractions (2). Epinephrine and norepinephrine levels rise during labor. Catecholamines are released from the adrenal medulla, and this release is associated with nausea, vomiting, increased blood pressure and decreased uterine blood flow (5,6). Analgesia can be provided via three routes: topical, enteral and parenteral (6). Pharmacologic analgesia comprises inhalation agents such as nitrous oxide and sevoflurane, parenteral narcotic agents such as pethidine (meperidine), fentanyl, tramadol, butorpha-

nol, remifentanil and ketamine and regional analgesia (6-8). Opioids are the most commonly used medications for treating pain and are frequently available in injectable form. These agents cause neural system depression, blocks neuronal transmission, thereby decrease pain. All opioids are associated with side effects such as respiratory depression, nausea, vomiting, euphoria or sedation (9). These drugs cross the placenta in large fractions and might reduce fetal heart rate variability (9). It is advised that these agents should be used with caution because of the risk of neonatal respiratory depression. Their use should be withheld in circumstances such as non-reassuring fetal heart rate patterns, maternal respiratory problems or maternal oxygen saturations lower than 95%.

Pethidine, also known as Meperidine, is a worldwide used analgesic for treating labor pain (9,10). Pethidine (Aldolan ™) decreases acute pain for 2-4 hours and is considered a good option to treated labor pain (11). However, the potential maternal and neonatal side effects of its active metabolite Norpethidin is concerning. The aim of this study is to evaluate the effect of pethidine injection on the duration of the active phase of labor, labor pain and maternal-neonatal outcomes.

Methods

The present study was performed prospectively between July 2017 and June 2018 at an inpatient setting of our Obstetrics and Gynecology Department at a Tertiary Training and Research Hospital. The study protocol was approved by the institution's ethics committee and registered to ClinicalTrials.gov (NCT03882814). Data from 240 patients in active labor were acquired during the study. Inclusion criteria were nulliparous and multiparous patients with singleton pregnancies between 37 and 41 completed weeks (according to the last menstrual period).

Exclusion criteria were maternal respiratory rate < 8 /min, maternal bradycardia (<60 bpm), major fetal congenital anomalies, uterine scar presence from previous pregnancies, malpresentation, antepartum haemorrhage, multiple pregnancies, labor induction, any chronic systemic disease, prolonged rupture of fetal membranes, and application of epidural analgesia.

Written informed consent was acquired from each participant. Eligible participants were accepted at the beginning of active labor phase, which was defined as the presence of spontaneous regular uterine contractions and cervical dilatation >4cm. The patients who received pethidine injection were included in the study group, and who was included in the control group received a placebo injection. The placebo injection was performed to control group to ensure the same measurement times as pethidine group.

A partogram was recorded throughout the labor. The digital cervical examination was performed and recorded at two-hour intervals regularly. Pethidine 50 mg intramuscular (IM) injection was performed when cervical dilatation was 4 cm or more than 4 cm and the cardiotocogram uterine contraction recordings of 200 Montevideo units. Blinded clinicians recorded the durations of first, second and third stages of labor, maternal vital signs at 0-5-15-30-45-60 minutes following pethidine injection, maternal complications and neonatal APGAR scores. There were no operative deliveries or delivery complications in both groups.

Amniotomy was performed routinely without PROM when the cervical dilatation reached >4cm. Opioid analgesia (pethidine HCl-50 mg I.M.) was given following amniotomy. Continuous fetal monitorization was performed throughout the labor. Labor augmentation with oxytocin was performed in patients with inadequate contractions, and these participants were excluded from the study. Additionally, in both groups those who delivered within 3 hours after pethidine administration were excluded from the study because the 2nd-hour VAS scores could not be evaluated in these patients.

In both groups, the VAS scale was utilized to determine labor pain, in which a score of 0 represented no pain and a score of 10 represented maximal pain. VAS score just prior to medication was recorded as the 0. Hour (initial) score, and 1st and 2nd-hour scores were recorded afterwards. The participants were subgrouped according to pain VAS scores; mild pain (1-3), moderate pain (4-7) and severe pain (8-10). Data regarding maternal age, parity, labor duration, and presence of maternal side effects such as numbness, dizziness, nausea/vomiting, respiratory depression, itching, hypotension (BP<90 mmHg or <20% of the initial values), bradycardia (HR<60 bpm) were recorded.

A neonatologist, an anesthesiologist and resuscitation equipment were ready at all times throughout labor and delivery. Neonatal outcomes in terms of 1st and 5th minute APGAR scores and resuscitation requirements were also recorded. Neonatal factors that may influence APGAR scores such as small for gestational age (SGA) presence, meconium aspiration syndrome and undiagnosed major fetal anomaly were recorded and these patients were excluded from the study.

Study data were recorded into a computer and analyzed using IBM Statistical Package for the Social Sciences version 20 (SPSS Inc., Chicago, IL, USA) software. Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as number and percentage. Kolmogorov Smirnov test was used to determine normal distribution. Mann Whitney U or Student's t-test was used to compare means. Chi-square or Fisher's exact tests were used to compared categorical variables. P values less than 0.05 were considered statistically significant.

Results

The study group received pethidine injection comprised of 132 patients and the control group (placebo injection) comprised of 108 patients. Thirty patients from the study group and sixteen patients from the control group were excluded from the study due to need for cesarean section (protracted or arrested labor and fetal distress), delivery at less than 3 hrs, presence of abnormal fetal conditions that may influence APGAR scores such as meconium aspiration syndrome. After the exclusion of these patients, 102 remained in the Pethidine group and 92 patients remained in the control group (Figure 1).

Maternal ages were statistically similar in both groups. Data including gravidity, parity, body mass index (BMI), gestational age, presence of premature rupture of fetal membranes (PROM) and the number of nulliparous pregnant women data are presented in Table 1. The active phase of labor was significantly shorter in the Pethidine group ($p<0.05$) (Table 2).

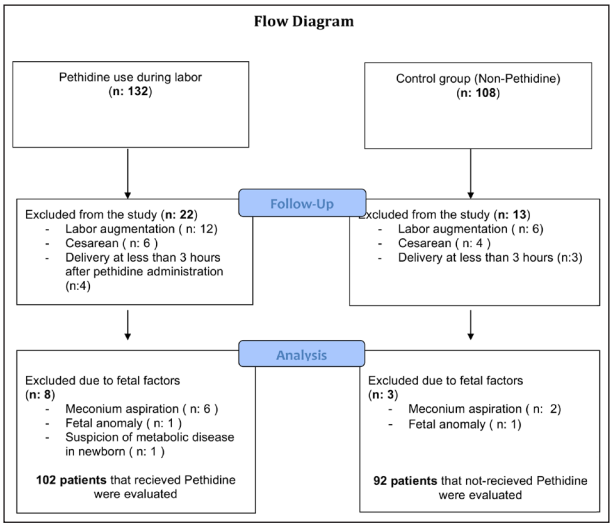

Figure 1. Flowchart of case and control group

Table 1. Characteristic and demographic features of the patients.

	1.Group / Pethidine (n : 102) Mean SD	2.Group / Controls (n : 92) Mean SD	*p* value
Age (years)	29.87.1 (17-42)	29.05.3 (20-41)	0.390
BMI (kg/m^2)	33.45.3 (23.5-54.4)	35.25.2 (21.8-46.6)	0.087
Gestational age (weeks)	38.61.61 (37-41.4)	38.71.49 (37-42)	0.534
Gravidity	1.981.21 (1-6)	2.431.64 (1-6)	0.063
Parity	1.14 (0-4)	1.221.39 (0-5)	0.072
Occurence of spontaneous PROM	28 (27.5%)	33 (38.4%)	0.111
Number of nulliparous pregnant women	41 (40.1%)	37 (38.9%)	0.245

***Sd** : standard deviation, **BMI** : body mass index, **PROM:** Premature Rupture of Membranes*

Table 2. Mean duration of stages of labor**.**

Stage of Labor	1.Group / Pethidine (n : 102) Mean SD	2.Group / Controls (n : 92) Mean SD	*p* value
First stage: Active phase (4-10cm) (minutes)	161.3098.17 (15-800)	182.09131.28 (20-660)	**0.001**
Second stage (10 cm - delivery) (minutes)	33.4627.27 (5-115)	28.6626.40 (5-1)	0.249
Third stage (delivery – placental detachment) (minutes)	15.254.06 (5-20)	15.982.7 (5-25)	0.151

***Sd** : standard deviation*

Labor pain was determined with VAS scores in both groups just prior to pethidine injection (0. hour), and 1st and 2nd hours after injection. Initial (0. hour) VAS scores were similar among both groups, however, 1st and 2nd-hour VAS scores were significantly less in Pethidine injection group ($p<0.05$) (Tables 3 and 4). Mean pain scores reduced from 7.55±1.21 to 5.73±1.54 at 1st hour and reduced from 8.38±1.22 to 5.16±1.29 at 2nd-hour evaluation.

Maternal heart rate, systolic and diastolic blood pressure values among groups before and after medication are presented in Table 5. Although the values were significantly lower in the study group, these values were in the normal range. Systolic and diastolic blood pressures were statistically similar in both groups.

Of the maternal side effects, nausea and vomiting occurred in 11 (10.7%) in study patients. Both groups were similar in terms of maternal side effects. Neonatal APGAR scores were similar in both groups. None of the newborns had respiratory depression that required resuscitation or neonatal intensive care unit admission.

Table 3. Mean Pain VAS Scores (0-10) in active phase of labor between two groups.

	0. hour Mean SD	1 st hour Mean SD	2 nd hour Mean SD
1. group / Pethidine	6.131.76	5.731.54	5.161.29
2. group / Controls	6.331.01	7.551.21	8.381.22
***p* value**	0.359	**0.001**	**0.001**

VAS: Visual analogue scale; Verbal pain score scale (0–10, 0= no pain, 10=severe pain), ***SD** : standard deviation*

Table 4. Pain intensity at different stages of the active phase between two groups.

	1.Group / Pethidine (n : 102) (%)	2.Group / Controls (n : 92) (%)	*p* value
0. hour			
Moderate Pain (1-3)	4 (4%)	0 (0%)	0.060
Mild Pain (4-7)	61 (59.8%)	61 (70.9%)	0.111
Severe Pain (8-10)	37 (36.3%)	25 (29.1%)	0.295
1 st hour			
Moderate Pain (1-3)	3 (2.9%)	0 (0%)	0.109
Mild Pain (4-7)	81 (80%)	35 (40.7%)	**0.001**
Severe Pain (8-10)	18 (17.6%)	51 (59.3%)	**0.001**
2 nd hour			
Moderate Pain (1-3)	5 (5%)	0 (0%)	0.07
Mild Pain (4-7)	93 (92.2%)	17 (19.8%)	**0.001**
Severe Pain (8-10)	4 (4%)	69 (80.2%)	**0.001**

Verbal pain score scale (0–10, 0= no pain, 10=severe pain)

Table 5. Mean Heart Rates, Systolic and Diastolic Blood Pressures in the minutes before and after pethidine administration in both groups.

	0 min	5 th.min	15 th.min	30 th.min	45 th.min	60 th.min
	Mean SD	**Mean SD**	**Mean SD**	**Mean SD**	**Mean SD**	**Mean SD**
Heart Rate						
Group-1	82.8	82.15.7	81.4	81.35.4	80.43.6	80.25.4
Group-2	81.05.2	81.04.9	82.54.9	82.54.8	84.44.8	84.54.9
***p* value**	0.070	0.526	0.187	**0.001**	**0.001**	**0.001**
Systolic blood pressure (mm Hg)						
Group-1	113.69.7	113.110.7	112.89.2	111.8	9.9	110.9
Group-2	112.39.1	111.313.2	114.48.7	115.3	115.88.3	115.68.5
***p* value**	0.291	0.312	0.227	0.07	0.08	0.06
Diastolic blood pressure (mm Hg)						
Group-1	75.18.6	8.2	748.8	739.1	68.98.1	9.0
Group-2	74.39.6	72.69.0	8.1	9.5	9.2	10.0
***p* value**	0.564	0.186	0.794	0.915	0.706	0.915

***Min**: minute, **SD** : standard deviation*

Discussion

It is considered challenging to compare the analgesic effect of the medications due to the subjective nature of evaluation. Alongside, the previous studies have demonstrated that pethidine is an effective analgesic that can be used to alleviate obstetric pain, especially the acute pain of labor (3,9). It is important to treat labor pain in obstetrics practice, and due to challenges of epidural analgesia, intramuscular application of pethidine is considered as a simpler and a less invasive alternative.

All pharmacologic measures used for intrapartum analgesia have possible disadvantages. Maternal side effects such as sedation, respiratory depression, delayed gastric emptying, nausea and vomiting might be associated with the use of pethidine. In addition, pethidine easily crosses the placenta and might cause complications such as respiratory depression and low APGAR scores in the newborn (9,12). In a previous study that 75 mg pethidine was used, this dosage was shown to be equally effective as 100 mg tramadol and 10 mg morphine (13). Pethidine use is more effective in relieving pain than tramadol at 30th and 60th minutes after injection (13,14). In another study, 75 mg pethidine applied intramuscularly is significantly more effective than placebo. In addition, there were no significant differences in terms of the intensity and frequency of the uterine contractions (12). There were also no significant deleterious effects regarding maternal blood pressure, heart rate, respiratory rate, newborn heart rate and APGAR scores after the injection. It has also been shown that pethidine is an effective medicine to provide maternal sedation (12).

A number of controlled studies demonstrating the analgesic effect of pethidine in treating labor pain is present in the literature (3,15,16). The studies show that pethidine does not have any effect on uterine contractions and that it provides sedation effect on the mother, providing therapeutic rest between contractions (17). The analgesic method provided is important, as shortening the duration of the active phase of labor means shortening of the duration of pain perception (1,18). Favilli et al. In their study, they evaluated women's preferences for pain and delivery time by applying a standardized questionnaire. Showed that patients were both focused on relieving pain during labor and delivery time (19). In our present study, according to the visual analogue scale scores that we used to determine pain, it was demonstrated that the pain during labor and the duration of the active phase

of labor was significantly reduced. In this setting, we demonstrated that pethidine had an expediting effect on labor, and besides reducing pain intensity, it also reduced the duration of pain. Although nearly all deliveries were completed nearly 3 hours after application of the analgesic, in another study that used a similar pethidine dose demonstrated longer labor durations. In this study, only in 10 out of 45 patients delivered 4 hours after analgesic application and delivery duration were not affected due to pethidine use (13).

Epidural analgesia is a very popular method during delivery in recent years. The general expectation of the patients the delivery is painless and short delivery period. It is also one of the biggest concerns in postpartum deformation in the genital area and urinary incontinence. epidural analgesia was associated with a prolonged II stage, use of oxytocin and episiotomy rate (19). In another study, The effect of epidural analgesia does not affect the onset of postpartum urinary incontinence in medium-term, regardless of the mode of delivery (20). We think that epidural analgesia, which has been popular in recent years, is not superior to pethidine because it prolongs labor. In our study, we showed that the birth time was not affected by the use of pethidine.

In a study that pethidine was used during labor, 64% of the participants experienced at least one of the side effects such as dizziness, blurred vision, dry mouth, dyspnea, tachycardia, vomiting and significant changes in blood pressure (18). In a study that compared pethidine 75 mg with tramadol 100 mg, the incidence of side effects such as nausea, vomiting, fatigue and numbness was significantly higher in the pethidine group (21). Use of pethidine for obstetric analgesia was reported to have no significant effects on maternal blood pressure and heart rate (21). Although a study that investigated maternal and fetal side effects of another opioid fentanyl reported fewer side effects of this drug, another study demonstrated that pethidine was more frequently selected for use in obstetric clinical practise (22-24). In a study performed in 2013, it was found that in patients that fentanyl was used, maternal heart rate was significantly lower when compared with controls (25). Although systolic and diastolic blood pressures were lower following IV injection of opioids in all periods, there were no significant differences among study groups (25). In the present study, the most commonly encountered side effects after IM use of pethidine were nausea and vomiting. However, the incidence of these side effects was similar between the study group and the control groups. Therefore, it can be stated that IM pethidine use during the active phase of labor is safe in terms of maternal side effects. Measurements of maternal heart rates, systolic and diastolic blood pressures support this statement, and no problems were encountered during labor in the present study.

Pharmacology references claim that, after application of pethidine doses lower than 100 mg during labor, the newborn was not affected if delivery occurred less than 1 hour or more than 4 hours after administration of the drug (26-28). The half-life of pethidine and its active metabolite norpethidine in the newborn varies between 36 and 48 hours (29). Studies on that investigate the side effects of pethidine on newborns mainly focus on problems in the first minutes after delivery (29,30). The most commonly reported side effects of pethidine on newborns are low APGAR scores and respiratory depression shortly after delivery (29). In a study that compared the newborns of patients that received pethidine injection with patients who did not receive any analgesics or anaesthesia, 5th minute APGAR scores were similar between the two groups (30). In another study, newborns of pethidine receiving mothers and controls were similar in terms of 5th minute APGAR scores, however, 1st-minute scores were significantly different (31). However, there are also studies which reported that 1st minute APGAR scores were similar between the opioid group and control groups (11). In the present study, no differences in terms of APGAR scores were found among the groups. All neonates of the 102 patients that received pethidine were examined by a neonatologist following delivery, none of these neonates had respiratory depression that required resuscitation. Although the rate of respiratory depression is variable, delivery within the 1st hour after administration is considered safe, and side effects are most commonly observed 3 to 5 hours after administration (29).

A study focusing on the effect of pethidine on newborns failed to demonstrate any significant differences on heart rate, oxygen saturation and blood

pressures within a 24 hours period (32). In the present study, heart rates, oxygen saturation and blood pressures of the neonates were recorded in a 24 hours period, and no differences were observed. Longer observations may be performed for breastfeeding problems that are encountered in patients that received pethidine, which is due to weaker suction reflex in these newborns. In the present study, the newborns were followed up within a 24 hours period, and long-term effects were not evaluated, which is one of the limitations of this study. In addition, the absence of blood gas results of newborns and the low number of patients are among the limitations. Strengths of the study; -it is a prospective case-control study, -birth and newborn follow-up by the same team, -besides the effect of pethidine on the duration of delivery, its maternal and neonatal effects were also investigated.

In conclusion, pethidine is a preferable analgesic because it reduces labor pain without an adverse effect on uterine contractions, it is readily available in most health care units and it is inexpensive. In addition to its clear analgesic effect, it can also reduce the duration of the active phase of labor. No major maternal or fetal side effects were demonstrated. Therefore, in the light of studies with larger sample sizes, we presume that pethidine may be considered for routine use for labor analgesia.

Clinical Trials Number: NCT03882814

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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