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Original Article

The Comparison of Patient-Controlled Remifentanil Administered by Two Different Protocols (Bolus and Bolus+Infusion) and Intramuscular Meperidine for Labor Analgesia

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Abstract

Objective: Nowadays, there are many pain relief methods for reducing the pain and stress of labor and delivery. In our study, two different remifentanil protocols (bolus and bolus+infusion) administered by patient-controlled analgesia method were compared with intramuscular meperidine for labor analgesia.

Methods: Ninety parturients who were scheduled for vaginal delivery were included in this study. Patients were randomly divided into 3 groups, with 15 primiparous and 15 multiparous patients in each group. Whenever a patient requested analgesics during the labor, Group M was given 1 mg kg^{-1} intramuscular meperidine, Group B was given intravenous bolus patient-controlled remifentanil, and Group IB was given intravenous bolus+infusion patient-controlled remifentanil. Patients' systolic and diastolic blood pressure, heart rate, pain-comfort and sedation scores, remifentanil consumption, side effects, and Apgar scores of the newborns were evaluated during the labor and delivery.

Results: Patients' mean pain and comfort scores were significantly lower in Groups B and IB than in Group M at all time intervals except the first minute. Compared with Group IB, mean pain and comfort scores at 15, 30, 60, and 120 minutes were significantly higher in Group B. The mean sedation scores were similar among the groups. Total remifentanil consumption was lower in Group IB than in Group B, but it was not statistically significant.

Conclusion: Patient-controlled intravenous bolus or bolus+infusion remifentanil provided more effective analgesia and patient comfort than intramuscular meperidine for labor analgesia. Especially during labor, bolus+infusion remifentanil administration provided better pain and patient comfort scores than bolus alone, without increasing remifentanil consumption.

Key Words: Labor analgesia, remifentanil, meperidine, patient-controlled analgesia

Introduction

Currently, labour is one of the well defined and known sources of sharpest pain (1). Today, epidural or combined spinal-epidural anaesthesia is the most commonly used and the most effective analgesia method used during vaginal delivery (2, 3). However, in case these methods are contraindicated (coagulation defects, anticoagulant use, patient's refusal, etc.), intramuscular (IM) or intravenous (IV) analgesia methods can be used.

Although IM meperidine administration, which is one of the traditional methods in Turkey, can provide acceptable analgesia during labour, it may cause neonatal depression particularly when used at high doses and close to delivery (4). In this sense, IV patient-controlled analgesia (PCA) has been introduced as an alternative for labour analgesia instead of intramuscular methods in the recent years and has gained popularity among this group of patients (5).

Although many opioid and non-opioid agents have been used by patient-controlled analgesia method for labour analgesia, remifentanil appears to have significant advantages owing to its rapid onset of action, short half-life and non-cumulative effects on foetus (6). However, rapid high dose infusion of remifentanil may cause respiratory depression. Despite our knowledge on the efficacy and safety of bolus or bolus plus infusion of remifentanil for patient-controlled analgesia in pregnant women is limited; there is either inadequate literature information on the efficacy of PCA in labour analgesia as compared to IM meperidine.

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The present study aimed to compare patient-controlled remifentanil application by two different methods (bolus or bolus plus infusion) and IM meperidine in labour analgesia.

Methods

After obtaining approval of Faculty Ethics Committee (Çukurova University Medical Faculty, date: 23.12.2010, decision no: 15) and verbal and written informed consents of the cases, a total of 90 (45 primiparous and 45 multiparous) expectant mothers in the American Society of Anaesthesiologists (ASA) I-II group with a mean gestational age of 270±10 days, and without any gestational pathology, who were planned for vaginal delivery, were enrolled in the study. Obese (BMI>40) and high risk (preeclampsia, severe asthma, insulin-dependent diabetes, hepatorenal disease) cases, as well as cases with a history of opioid allergy, long-term opioid use or chronic pain, were excluded from the study.

Cases enrolled in the study were first informed about pain, sedation and patient comfort scales, the use of infusion pump, and the procedures that are going to be implemented. Vascular access was achieved by a 20 gauge IV cannula in the expectant mothers that were admitted to the clinic for delivery and Ringer Lactate infusion was started at a rate of 1-3 mL kg^{-1} h^{-1}. The expectant mothers were monitored by means of non-invasive blood pressure, electrocardiography and pulse-oximeter over the course of labour and delivery. In addition to demographic data (age, weight, gestation period, and labour period), systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and heart rate (HR), respiratory rate (RR) and peripheral oxygen saturation (SpO_2) values were monitored and recorded for all patients. Airway equipment (ambu, oxygen mask, laryngoscope, and intubation tube) was made available for all cases in case of respiratory depression.

The cases were assigned to meperidine (Group meperidine= M), bolus remifentanil (Group Bolus= B) or infusion plus bolus remifentanil (Group infusion plus bolus= IB) groups using a computer based randomization method in the way that each group would include 15 primiparous and 15 multiparous pregnant women. For remifentanil infusion, 2 mg remifentanil was added into 100 mL of 0.9% saline and thus 0.02% remifentanil solution (20 μg mL^{-1}) was prepared. Intravenous PCA device (Body Guard 575, Pain Manager Provider) was programmed to deliver a bolus dose (0.25 μg kg^{-1}) or infusion plus a bolus dose (0.025 μg kg^{-1} hr^{-1} continuous infusion plus 0.25 μg kg^{-1} bolus) of remifentanil with a lock-out time of 2-minutes. Preparation of remifentanil solution and installation of the device were done by an anaesthesiologist who was blinded for the study groups.

In the event that expectant mothers demanded analgesics during labour (VRS score >3-4), pain treatment was started with 1 mg kg^{-1} of IM meperidine in Group M, with patient-controlled bolus dose of (0.25 μg kg^{-1}) remifentanil following a loading dose of 0.25 μg kg^{-1} in Group B, and with patient-controlled infusion plus bolus doses (0.025 μg kg^{-1} h^{-1} infusion + 0.25 μg kg^{-1} bolus) of remifentanil following a loading dose of 0.25 μg kg^{-1} in Group IB.

Pain level was assessed by verbal rating scale (VRS; 0= no pain, 10= the worst possible pain imaginable); level of sedation was assessed by a five-point sedation scale (1=fully awake, 2=mild sedation, 3=lethargic, 4=sleeping, but can be awakened, 5=deep sleep, cannot be awakened); and patient satisfaction was assessed by patient comfort scale (0=comfortable, 10=extremely uncomfortable). In all cases, VRS, patient comfort and sedation scores, SAP, DAP, HR, RR and SpO_2 values, number of demanded and administered bolus doses of remifentanil and total amount of remifentanil administered were recorded at 1, 15, 30, 60 and 120 minutes, and at the time of delivery. Adverse effects such as respiratory depression, hypotension, nausea, vomiting, and chilling and shivering were questioned over the course of study and were recorded. A SAP <100 mmHg or a decrease of 30% of the baseline value was considered as hypotension. In this case, IV fluid infusion in combination with repeated doses of IV ephedrine (10 mg) was administered until blood pressure was elevated to baseline values. A HR<60 beats min^{-1} was considered as bradycardia, and 0.5 mg IV atropine was administered in the event of a heart beat rate<50 beats min^{-1}. After delivery was completed, patient-controlled analgesia was terminated. All new-borns were evaluated for 1- and 5-minute Apgar scores by a neonatologist, who was blinded for the groups that the new-borns were belong to, and the data were recorded.

Statistical analysis

Power analysis was performed to determine the number of patients that would be enrolled in the study. Since the aim of the study was to evaluate the efficacy of the methods used for labour analgesia, the primary goal was to achieve 25% decrease in pain scores (VRS). In power analysis, the number of cases necessary to test the hypothesis with α=0.05 and β=0.8 values was determined to be 30 for each group. Data were analysed by SPSS package program. Values were presented as mean±standard deviation (Mean±SD). Histograms of the group were generated and it was determined that they showed normal distribution. While one way ANOVA and Student-t test were used for inter-group analyses, repeated measures analysis was used for multiple repeated measures (intra-group). A P value <0.05 was considered to show statistically significant differences.

Results

No significant difference was found between the groups in terms of age, weight, gestation period and labour period (p>0.05) (Table 1). It was determined that SAP and HR of the cases during delivery were statistically significantly higher in Group M as compared to group IB, but similar in both groups in the other time periods (Table 2). Respiratory rate during delivery was statistically significantly lower in Group B and Group IB than that of Group M (p<0.05) (Table 2).

SpO_2 values were above 95% in all cases over the course of study.

Mean pain (VRS) and patient comfort scores were significantly lower in Group B and Group IB as compared to Group M in all time periods except for the 1st minute. Compared with Group IB, it was determined that these scores were statistically significantly higher in Group B at 15, 30, 60 and 120 minutes ($p<0.05$) (Table 3). However, mean sedation scores were similar between the groups ($p>0.05$) (Table 3).

Although demanded and administered bolus doses and overall doses (loading plus bolus plus infusion) used in the groups that received remifentanil were lower in Group IB as compared to Group B, the difference was not statistically significant ($p>0.05$) (Table 4).

No difference was determined between the groups in terms of 1- and 5-minute Apgar scores ($p>0.05$). Respiratory depression was not determined in any of the new-borns and there was no need for opioid antagonists (naloxone). None of the expectant mothers enrolled in the study developed adverse events such as hypotension, bradycardia, respiratory depression, nausea or vomiting over the course of the study period.

Table 1. Age, weight, gestation and labour periods of the groups (Mean±SD)

	Group M	Group B	Group IB
Age (years)	26.6±4.6	25.4±4.6	25.6±4.6
Gestational period (days)	274±5.5	278±3.6	275.6±3.4
Weight (kilogram)	72.8±9.5	73.9±7.6	74.1±7.0
Labour period (minute)	166.6±34.7	170.1±23.8	169.1±25.1

SD: standard deviation

Discussion

Today, patient-controlled analgesia is an effective and popular analgesia method for the treatment of pain during labour. However, it is desired for the analgesic agent, which would be used for this purpose, not to have a cumulative effect, have rapid onset of action and not to cause adverse events in the foetus. In this sense, remifentanil is superior to other analgesics. Its action starts in 30-60 seconds and reaches to maximum analgesic efficacy in 60-80 seconds (7). Its half-life is 3-5 minutes regardless of infusion time and is rapidly degraded by plasma and tissue esterases (8, 9). Although it passes through the placenta, it is rapidly metabolized by the foetus (10). However, it may have dose-dependent adverse effects such as respiratory depression, and decreased heart beat rate, blood pressure and cardiac output (6, 10, 11). Owing to these characteristics, remifentanil is preferred either as an additional analgesic agent to general or regional anaesthesia during caesarean section or as a primary agent for labour analgesia (12, 13).

In a recent multicentre survey, it was reported that PCA was preferred by 47% for analgesia in pregnant women who did not receive epidural anaesthesia and that remifentanil was the most commonly preferred agent although numerous opioid agents have been used for this purpose (14). Tveit reported that patient-controlled IV remifentanil might be an alterna-

Table 2. SAP, DAP, HR and RR of the groups (Mean±SD)

	1st minute	15th minute	30th minute	60th minute	120th minute	Labour
SAP (mmHg)						
Group M	123±6.5	119±8.4	120.1±7	120±8.5	123±7.6	128±8.2*
Group B	123.1±5.5	116.5±4.0	117.1±5.5	116.5±6.5	120±5.7	121.1±3.1
Group IB	125±5.6	115±4.2	115±5.1	114±5.3	117.3±5.5	118.4±3.6
DAP (mmHg)						
Group M	75.4±5.9	76.1±5.5	75.6±5.1	76.5±4.6	76.8±4.8	80.3±5.4
Group B	77.6±4.2	75.6±3.8	75.6±2.9	76.3±1.6	74.5±3.9	77±3.1
Group IB	77.4±4.2	75.0±3.7	74.0±2.9	75.5±2.5	73.8±3.9	76±4.5
HR (beat min^{-1})						
Group M	90.3±11.8	88.1±10.7	88.6±11.2	87.8±9.8	88.8±10.9	92.0±12.1*
Group B	91.9±7.4	85.3±7.0	83.2±6.6	83.9±5.9	83.5±5.0	83.9±6.2
Group IB	91.7±5.9	83.1±6.4	81.4±6.2	82.3±6.1	81.8±5.5	82.3±6.0
RR (breath min^{-1})						
Group M	15.5±0.8	15.4±0.8	15.4±1.1	15.9±1.1	15.6±0.9	15.5±1.1*
Group B	15.4±0.9	14.6±1.1	14.4±0.9	14.6±1.2	14.5±1.1	14.2±1.0#
Group IB	15.2±0.9	12.6±1.1	12.9±1.3	12.8±1.3	13.0±1.2	13.4±1.1

*($p<0.05$) when compared with Group B and IB, one way ANOVA. #($p<0.05$) when compared with Group IB, student-t test; SD: standard deviation; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; HR: heart rate; RR: respiratory rate

Table 3. Pain (VRS), sedation and patient comfort scores of the groups (Mean±SD)

	1st minute	15th minute	30th minute	60th minute	120th minute	Labour
VRS						
Group M	9.0±1.0	7.0±1.0	6.4±1.1	4.1±1.0*	6.5±1.1	7.0±1.3
Group B	9.0±1.0	5.0±1.0 *	4.1±1.0*	6.4±1.1	4.3±1.0*	5.2±1.2*
Group IB	9.0±1.0	4.2±1.0*,α	3.0±1.0*,α	3.0±1.0*,α	3.0±1.0*,α	5.4±1.0*
Sedation						
Group M	1.0±0.2	1.4±0.6	1.7±0.7	1.7±0.7	1.7±0.7	1.6±0.2
Group B	1.0±0.0	1.6±0.6	1.6±0.6	1.6±0.6	1.6±0.6	1.6±0.4
Group IB	1.0±0.0	1.8±0.7	1.8±0.7	1.9±0.7	1.9±0.7	1.5±0.5
Comfort						
Group M	7.0±1.5	6.1±1.1	6.0±1.3	6.0±1.3	6.0±1.3	6.0±1.2
Group B	8.0±1.2	5.0±1.1*	4.5±1.0*	4.5±1.0*	4.5±1.0*	4.5±1.0*
Group IB	8.0±1.2	4.4±1.0*	3.1±1.0*,α	3.0±0.7*,α	3.2±1.0*,α	4.5±1.0*

*(p<0.05) when compared with Group M, Student-t test. α(p<0.05) when compared with Group B, Student-t test; SD: standard deviation; VRS: Verbal Rating Scale

Table 4. Bolus remifentanil and total (loading plus bolus plus infusion) remifentanil doses (μgr) demanded/administered in Group B and IB (Mean±SD)

	1st minute	15th minute	30th minute	60th minute	120th minute	Labour
Bolus (demanded)						
Group B	2.0±0.4	9.1±2.0	18.0±3.0	35.2±3.0	60.5±6.1	88.1±14.5
Group IB	1.5±0.5	9.0±1.4	16.0±2.1	30.0±3.1	57.0±4.4	79.4±12.1
Bolus (administered)						
Group B	1.0±0.0	5.0±1.0	10.3±1.8	21.3±4.0	42.4±8.0	61.0±13.1
Group IB	1.0±0.0	5.0±0.7	10.2±1.0	19.5±3.0	38.2±5.0	56.1±10.3
Total						
Group B	20.1±2.0	101.0±17.5	208.0±38.3	452.3±71.1	867.0±148.0	1236.4±273.2
Group IB	20.1±2.0	98.5±14.1	213.0±31.3	411.2±59.5	807.0±108.0	1174.0±215.5

SD: standard deviation

tive to epidural analgesia owing to adequate labour analgesia, high maternal satisfaction and non-serious adverse effects. Contrarily, it was emphasized that remifentanil causes sedation and oxygen desaturation in mothers; therefore, cases should be closely monitored by experienced personnel during administration, and remifentanil needs to be preferred instead of morphine or meperidine for labour analgesia in the event epidural analgesia is not applicable (15).

In the present study, it was determined that more effective analgesia and higher patient comfort scores were obtained in the patients that received remifentanil by PCA method as compared to the meperidine group, and that these scores were better in Group IB as compared to Group B. Although the mean pain scores decreased in Group IB and Group B over the course of labour, it was observed that pain scores in these groups increased again in line with the increase in the intensity of pain during delivery and the difference between two groups, which was present until that time, statistically disappeared. Since pain during labour increases in line with the intensity of uterine contractions, bolus doses alone may be inadequate. In this sense, addition of bolus remifentanil doses to a predefined constant basal infusion may provide more effective and safer analgesia. It was thought that the reason for better analgesia scores in Group IB in comparison to Group B over the course of labour was better maintenance of plasma analgesic concentrations. However, it was observed that these doses remained inadequate during delivery in line with increased pain intensity and that VRS values could be kept just around 5 in both groups.

During patient-controlled analgesia applications, opioid agents can be used in the form of infusion, bolus or combination of both. There is no consensus on which method provides effective analgesia with the lowest adverse effect (16-18). Bolus dose administration alone may lead to fluctuations in plasma concentrations, whereas continuous infusion may lead to cumulative effects. In the literature, there

are different results concerning either method. Shen et al. (19) compared patient-controlled bolus remifentanil (0.1-0.4 μg kg^{-1}) with continuous remifentanil infusion (0.05-0.2 μg kg^{-1} min^{-1}) for labour analgesia and concluded that bolus remifentanil provides better analgesia. Roelants et al. (20) used 0.05 μg kg^{-1} min^{-1} basal infusion and 25 μg bolus dose by PCA following a loading dose of 50 μg IV remifentanil with 5-minute lock-out time for labour analgesia in expectant mothers and terminated remifentanil infusion when cervical dilatation was 10 cm and cervical effacement was 100%. They stated that effective and safe analgesia has been provided with the existing protocol that includes addition of basal infusion and that it might be an alternative to epidural analgesia. As is in the above-mentioned studies, safe dose range was reported to be 0.25-0.5 μg kg^{-1} for bolus administration and 0.025-0.05 μg kg^{-1} h^{-1} for infusion in the other studies that used remifentanil for labour analgesia (20-22). In the present study, bolus and infusion doses of remifentanil were kept within these ranges, which have been reported to be effective and safe.

Douma et al. (23) compared the efficacy of remifentanil, fentanyl and meperidine in labour analgesia and reported more effective analgesia but higher sedation, pruritus and desaturation in the mother with patient-controlled remifentanil as compared to fentanyl and meperidine. Therefore, continuous monitoring is of great importance while using patient-controlled IV remifentanil for effective dosing and respiratory depression risk (24, 25). In the present study, all cases were closely followed by continuous monitoring, and while pain scores were significantly lower in remifentanil groups, oxygen saturation values were found to be similar in each of the three groups. It was thought that these data on adverse effect profile are associated with safety dose range and lock-out period preferred in the present study.

Conclusion

It was concluded that, remifentanil, which is used for labour analgesia by patient-controlled analgesia method, has similar sedation and adverse effect profile with that of IM meperidine but provides more effective analgesia and patient comfort and infusion plus bolus remifentanil administration in comparison to remifentanil bolus administration alone provides more effective analgesia and patient comfort without consumption of higher amount of remifentanil particularly during labour.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Çukurova University Faculty of Medicine (23.12.2010, No: 15).

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