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Continuous infusion of Remifentanil plus Ketamine compared with continuous Remifentanil for pain relief in labor

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Abstract

Background: Pain relief during labor is an important determinant of a women's birth experience. There are numerous pain relief techniques which can be used either with or without pain medication. The aim of our study was to compare the effect of remifentanil alone and its effect in pain relief while using with ketamine during labor.

Methods: After obtaining informed consent and approval of hospital ethics committee, 40 women with gestational age between 38 and 42 weeks gestation in early labor were recruited for this study. They were randomly allocated into two groups: group RK (20 cases) received 25 μg remifentanil as a starting dose and continuous infusion of 0.06 μg/kg/min remifentanil plus 0.5 mg/kg/h ketamine for 4 hours via pump and group R (20 cases) received 25 μg remifentanil as a starting dose and continuous infusion of 0.06 μg/kg/min remifentanil.

Results: The baseline of pain scores were similar in both groups (5.75 ± 2.51 vs 7 ± 2.45, p= 0.12) but after 30 minutes to 120 minutes the VAS scores were significantly higher in R group (p< 0.001). The rate of patients who were satisfied (excellent and very good) in RK was 80% but in R group was 45% (p = 0.03). Nausea and vomiting were significantly higher in R group (p<0.05).

Conclusion: The remifentanil plus ketamine produced better pain relief during labor with continuous monitoring than continuous remifentanil with no adverse effects for mothers and infants.

Keywords: Remifentanil, Ketamine, Analgesics opioid, Obstetric.

Introduction

Pain relief during labor is an important determinant of a women's birth experience. There are several pain relief techniques which can be used either with or without pain medication. Most women request some form of pain relief during labor and it is important in order to reduce the demand for cesarean section. From various type of analgesia, regional blocks have been shown to be most effective [1].

However, in some of the cases it may be contraindicated or technically impossible or may not be chosen. In such cases other forms of pain relief like breathing exercises, transcutaneous nerve stimulation and opioids, either intramuscular or intravenous can be used.

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Remifentanil as a potent, short-acting μ-opioid agonist and chemically related to fentanyl [2] has major advantages over other opioids such as its rapid onset of action and rapid clearance rate by red blood cells [3].

In a pilot study, Thurlow et al showed that remifentanil gave a better pain relief by patient-controlled analgesia (PCA) to mothers in labor than intramuscular meperidine [4].

Ketamine is an N-methyl-D-asparate (NMDA) receptor antagonist with analgesic properties in subanesthetic doses it has the potential to reduce opioid consumption [5, 6].

Two studies concluded the addition of ketamine to bupivacaine or thiopentone for caesarean section had benefit of reducing analgesic requirement without any side effects [7,8]. A recent study in 2010 showed that infusion of low dose ketamine provided an acceptable labor analgesia with good neonatal outcomes [9].

Therefore, the objective of our study was to compare the effect of remifentanil plus ketamine and remifentanil alone in pain relief during labor.

Methods

After obtaining approval of hospital ethics committee, 40 women aged between 18 and 40 years, nulliparous, ASA I, II, between 38 and 42 weeks of gestation in early labor were recruited for this clinical trial study. Written informed consent was obtained from all participants. Women weighing less than 50 kg, more than 100 kg, or planed to use epidural analgesia were excluded. Other exclusion criteria were multifetus pregnancy, pre-eclampsia, premature labor, allergy to any agent under investigation and a history of alcohol or drug abuse and psychiatric disorder. All women were in active labor (cervical dilation of 4 - 5 cm).

The women were randomly allocated into two groups by sequentially numbered, sealed opaque envelopes prepared by an independent practitioner. The RK group parturients (20 cases) received a bolus 25-μg dose of remifentanil (Ultiva, Glaxo Smith Kline, Italy) followed by a continous 0.06 μg/kg/min infusion plus 0.5 mg/kg/h ketamine (ROTEXMEDICA, TRITTAU, Germany) for 4 hours (maximum dose of ketamine 2mg/kg) via pump (Accufuser, Woo Young Medical Co., LTD, Korea). If delivery did not happen by four hours, we continued only remifentanil in the same dose. The R group parturients (20 cases) received a bolus 25-μg dose of remifentanil followed by a continous 0.06 μg/kg/min infusion.

All women had an inserted i.v. cannula (minimum 18-gauge) and an erected i.v. fluids to run at 70 ml/h. A 20-gauge i.v. cannula was also inserted for pump infusion. Nasal oxygen was administered for all patients by the dose of 3 liter/minutes. Non-invasive arterial pressure monitoring and pulse-oximetry were established. Arterial pressure, heart rate, SpO_2, respiratory rate, observer sedation score (1= fully awake; 2= drowsy; 3= eye closed but responsive to voice; 4= eye closed but unresponsiveness), fetal heart rate, and presence or absence of nausea and vomiting were recorded. Pain was assessed with a continous visual analogue scale (VAS; 100 mm, marked '0 mm = no pain' to '100 mm = worse pain imaginable'). Participants were asked to mark on the line the worst pain they had felt during their last contraction after it had finished.

Baseline recordings were made and then measurements were taken every 30 min after starting analgesia. Although measurements were recorded every 30 min, all participants were observed throughout by an anesthesia nurse and one of the investigators in the delivery suite at all times during the study.

Surface ultrasound utilized in order to continous FHR monitoring, and 1- & 5-min Apgar scores were recorded upon delivery. The overall effective analgesia was rated after delivery by the mother within 2 h of delivery on a five point verbal scale ranging from excellent to poor (Likert scale: 5= Excellent, 4= very good, 3= good, 2= fair, 1= poor).

An adverse event was defined as a respiratory rate < 8 breaths/min, SpO_2 < 90% for

Table 1. Patients' and labor characteristics

	Group RK	Group R	p value
	(n = 20)	(n = 20)	
Age (yrs)	25.1 ± 4.27	24.75 ± 5.22	0.82
BMI (kg/m2)	27.23 ± 3.47	27.44 ± 3.04	0.85
Gestational age (wks)	39.2 ± 1.82	39.05 ± 1.54	0.78
Oxytocin use	16 (80)	25 (83.33)	0.76
Duration of first stage (min)	181.5 ± 81.47	366.84 ± 207.58	0.0007
Duration of second stage (min)	29 ± 22.28	45.75 ± 23.91	0.03
Apgar score			
1 min	8.84 ± 0.69	8.85 ± 0.49	0.97
5 min	9.95 ± 0.23	10 ± 0	0.31

Data are presented as mean ± standard deviation and number (percentages).
P value refers to t-test and χ^2-test when appropriate.

Table 2. Evaluation of complications, satisfaction and sedation score.

	Group RK	Group R	p value
Complication			
Nausea	4 (20)	13 (65)	0.004
Vomiting	2 (10)	11 (55)	0.002
Satisfaction			
Excellent	10 (50)	5 (25)	
Very good	6 (30)	4 (20)	
Good	4 (20)	9 (45)	
Bad	0 (0)	2 (10)	
Sedation			0.11
1	2 (10)	12 (60)	
2	8 (40)	8 (40)	
3	10 (50)	0(0)	
			0.0002
Minimum O_2 saturation	95.5 ± 1.05	95.35 ± 1.42	0.71

Data are presented as number (percentages) and mean ± standard deviation.
P value refers to t-test, χ^2-test and Fisher's exact test when appropriate.

more than 15seconds, mean arterial pressure < 75% of baseline, maternal heart rate < 50 beats/min, fetal heart rate sustained at < 110 beats/min or sedation score >3. If any adverse event persisted, the study was stopped, an appropriate treatment given and no further data recorded from the participants. Also the study was stopped if a woman was unwilling to continue or requested regional analgesia.

Statistical Analysis

Statistical analysis was performed with JMP software (Version 4; SAS institute, USA). Utilizing the standard deviations of VAS, pain scores were measured in labor for the 20 participants in each group. Using student's t-test and analysis of variance, the differences in average pain was detected. [10]. The student t-test and χ^2 test were used for comparisons of other outcome variables (as appropriate) between the RK and R groups. A two-tailed p-value of less than 0.05 was considered as statistically significant.

Results

Based on the Table 1, patient's characteristics such as age, body mass index (BMI) and gestational weeks were not significantly different between two groups (All P-values> 0.05). Meanwhile, the Apgar scores were similar in both groups. However, the duration of first stage and second stage of labor was significantly longer in group R (366.84 ± 207.58 vs 181.5 ± 81.47, p=

Table 3. Maternal observation before (baseline) and 30, 60, 90 and 120 minutes after starting analgesia for labor and VAS score.

	Group RK	Group R	p value
Systolic Blood Pressure (mmHg)			
Baseline	105 (10)	102 (11)	0.38
30 min	106 (15)	101 (10)	0.24
60 min	106 (15)	103 (10)	0.46
90 min	108 (17)	101 (9)	0.12
120 min	107 (15)	101 (11)	0.25
Maternal heart rate (beats/min)			
Baseline	88 (11)	91 (9)	0.51
30 min	91 (15)	92 (10)	0.71
60 min	92 (14)	94 (12)	0.64
90 min	97 (16)	94 (10)	0.57
120 min	91 (16)	94 (13)	0.46
Respiratory rate			
Baseline	19 (3)	20 (3)	0.47
30 min	18 (4)	20 (3)	0.14
60 min	18 (4)	19 (3)	0.17
90 min	19 (4)	20 (3)	0.39
120 min	18 (3)	20 (3)	0.14
Fetal heart rate (beats/min)			
Baseline	135 (7)	138 (5)	0.06
30 min	135 (7)	139 (6)	0.03
60 min	134 (8)	141 (9)	0.01
90 min	133 (8)	141 (8)	0.01
120 min	136 (9)	139 (8)	0.25
VAS score			
Baseline	5.75 ± 2.51	7 ± 2.45	0.12
30 min	2.50 ± 2.16	5.90 ± 2.22	< 0.001
60 min	2.80 ± 2.17	6.20 ± 2.04	< 0.001
90 min	2.79 ± 2.55	6.44 ± 2.53	< 0.001
120 min	2.73 ± 2.87	6.94 ± 2.33	< 0.001

Data are presented as mean and standard deviation. P value refers to Student's t-test.

0.0007; 29 ± 22.28 vs 45.75 ± 23.91, p= 0.03) compared to the RK group. Minimum oxygen saturation during the study was similar in both groups (Table 2). Nausea and vomiting in RK group participants (Table 2) were lower than in R group ones ($p < 0.05$). The number of fully awake or drowsy participants was significantly higher in R group (100% vs 50%) but the ones in grade 3 of sedation (eye closed but arousable to voice) were many more in RK group (50% vs 0%) (P=0.0002). There was no case in grade 4 of sedation in each group. The rate of satisfaction (excellent and very good) in RK and R groups were 80% and 45%, respectively (p= 0.03) (Table 2). Table 3 summarized that the systolic blood pressure, as well as pulse and respiratory rates in baseline, after 30, 60, 90 and 120 minutes were not significantly different between two groups. Fetal heart rate was significantly higher in R group after 30, 60 and 90 minutes but not after 120 minutes compared with RK group. The baselines of VAS scores were similar in both groups (50.75 ± 20.51 vs 70 ± 20.45 mm, p = 0.12) although was significantly higher in R group after 30 to 120 minutes (Table 4) ($p < 0.001$). No patients had hallucinations in RK group.

Discussion

In this study we compared two pharmacological regimens for pain relief during labor. We chose the same dose of remifentanil which Volmanen et al [11] showed as an effective dose without desaturation in labor. In addition, there is evidence suggesting that continuous infusions may produce less sedation than larger in-

termittent boluses [12]. In the present study a calculated weight-based dose was administered. However in other studies, an average dose of drug was administered rather than a calculated weight-based one [4,13]. Ideally it is better to administer the dose as necessary with progression of labor, especially as acute tolerance can develop with prolonged use of remifentanil [14].

Small dose ketamine has been shown to be a useful and safe additive to opioid analgesia [15] and it can improve postoperative analgesia [16,17]. Several studies showed that continuous IV small-dose ketamine infusion improved peri-operative opioid analgesia [18,19]. Ketamin has been used in pregnant patients, although its high doses (greater than 2 mg/kg) can produce psychomimetic effects and increased uterine tone. It may also cause low Apgar scores and abnormalities in neonatal muscle tone [20]. We added 0.5 mg/kg/h ketamine (maximum dose 2 mg/kg) to remifentanil in order to improve quality of analgesia during labor.

Maternal safety is a concern with any opioid-based analgesic technique including remifentanil during labor. Sedation score did increase over the time in this study. However, these increases in sedation were usually from “awake” to “drowsy” and all women remained “responsive to voice (grade 3)” throughout. The short duration of action and lack of accumulation of remifentanil imply that any problems with sedation would be quickly reversed [13].

Another concern with remifentanil proposes the threat of maternal respiratory depression. Our study confirmed that utilizing nasal oxygen for both “ketamine-remifentanil” and “just remifentanil”, episodes of desaturation did not occur. However Blair et al. reported some episodes of desaturation in remifentanil usage, although the majority of them also used Entonox throughout the study period. This may have contributed to the respiratory depression in that group [13].

The overall satisfaction in RK group was 80% compared to 45% in R group which was also statistically significant.

In our study the Apgar score was similar in both groups. Although the FHR showed significant differences between two groups after 30, 60 and 90 minutes, its averages were in the normal range (120-140) and the study was completed without obvious clinical side effects for infants.

Investigation of remifentanil pharmacokinetics in infants under 2 months provide an explanation of why the fetus is relatively unaffected by exposure to remifentanil: its half-life in this population was found to be equal to that in adults [21]. However, fetus is able to metabolize remifentanil crossing the placenta rapidly. This is one of the advantages of remifentanil compared to other opioids that have prolonged half-lives or problems with accumulation after prolonged exposure in neonates.

Guignard et al. showed continuous infusion of small-dose ketamine decreased remifentanil consumption without increasing the incidence of side effects [22]. In our study adding ketamine to remifentanil did not increase side effects, too.

Karamaz et al. showed that infusion of ketamine decreased the incidence of nausea and pruritus [18].

Conclusion

The combination of continuous remifentanil and ketamine with continuous monitoring produced better pain relief during labor than just continuous remifentanil with no adverse effects for mothers and infants. In addition our study showed that nausea and vomiting was occurred significantly less in ketamin-remifentanil group.

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