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Comparison of the Effect of Incremental Bolus and Incremental Infusion Regimens of Remifentanil on Labour Pain

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Background: Most pregnant women who deliver in obstetrics units require pharmacological or non-pharmacological pain relievers that could provide potent analgesic effects with least maternal and neonatal adverse effects.
Objectives: The aim of this investigation was to compare the efficacy and adverse maternal and neonatal effects of Remifentanil given by bolus patient-controlled analgesia (PCA) versus continuous intravenous (IV) infusion for labor analgesia.
Patients and Methods: This randomized, single-blind clinical trial was conducted on 82 nulliparous parturient women in the active phase of labor, admitted to Ali Ebn-e Abitaleb Hospital, Zahedan, Iran from January 2010 to March 2013. The participants were randomly assigned into two equal groups of 41. In the infusion group, patients received incremental Remifentanil IV infusion from 0.025 to 0.1 μg/kg/min. In the bolus group, participants received incremental PCA bolus Remifentanil from 0.25 to 0.4 μg/kg with a lock-out time of four minutes. Average Visual Analog Scale (AVAS) pain scores in stages 1 and 2, labor duration, adverse effects, neonatal outcomes, total amount of administered Remifentanil and maternal satisfaction were assessed.
Results: In both methods, the pain scores were significantly reduced after Remifentanil administration in both stages of labor ($P < 0.001$). There were no statistically significant differences in the pain intensity reduction between the groups ($P = 0.49$, $P = 0.36$, in the stages I and II of labor, respectively). There were no statistically remarkable differences between the two groups for labor duration ($P = 0.4$), neonatal outcomes ($P = 0.9$) and maternal satisfaction ($P = 0.8$). The total amount of administered Remifentanil was significantly lower in infusion group compared to bolus group ($P = 0.001$).
Conclusions: Remifentanil in both infusion and bolus methods could decrease labor pain in both stages without serious maternal or neonatal adverse effects and without increasing the duration of labor. The average dose of Remifentanil needed to reduce pain was significantly lower in the infusion method compared to the bolus method.

Keywords: Analgesia; Remifentanil; Pain

1. Background

Most pregnant women who deliver in obstetrics units require pharmacological or non-pharmacological pain relievers that could provide potent analgesic effects with least maternal and neonatal adverse effects (1). Neuraxial blockade is the gold standard for labor analgesia; however, when neuraxial analgesia is contraindicated, systemic analgesia is a reasonable alternative (2); in these cases a safe, effective and easy-to-administer systemic analgesic with rapid onset and offset that could match the time of uterine contractions is a good choice. Researchers have been always looking for an appropriate method to provide the maximum analgesic effect in minimum required doses for relieving the labor pain, without prolonging the duration of labor (2). Remifentanil is a potent, short-acting mu-receptor opioid agonist with a rapid onset of action and rapid clearance rate (3). Some recent studies indicated that Remifentanil patient-controlled analgesia (PCA) is less effective in pain reduction compared to the epidural analgesia (EA). While some other investigations suggested that satisfaction level with Remifentanil may be higher in parturient mothers (4, 5). Although most studies approved the modest analgesic effect of Remifentanil in the first stage of labor, the effect of Remifentanil in the second stage of labor still remains controversial (6, 7). Additionally, the appropriate dose and method of Remifentanil administration for reducing labor pain have not been established yet (8-11).

2. Objectives

Therefore, this study was performed to compare the analgesic efficacy of two different methods of Remifentanil administration (incremental PCA bolus and incremental infusion) on labor pain reduction in the first and second stages of labor. In addition, we assessed the effects of two treatment methods on maternal satisfaction, duration of the first and second stages of labor and fetal outcomes.

3. Patients and Methods

This randomized single-blind clinical trial was conducted from January 2010 to March 2013 at the Department of Anesthesiology of Ali Ebn-e Abitaleb Hospital, Zahedan, Iran to compare the efficacy of two methods of Remifentanil administration in parturient women. The main outcome was reduction of labor pain and secondary outcomes were maternal satisfaction, duration of the first and second stages of labor and the fetal outcomes. This study was approved by the Institutional Review Board of Zahedan University of Medical Sciences. This study was registered at the Iranian Registry of Clinical Trials (www.irct.ir), which is a Primary Registry in the WHO Registry Network (Registration Number: 2012100811020N2). Eighty two healthy primigravida parturient women aged 18 - 35 years with gestational ages of 37 - 40 weeks who requested labor analgesia were included in this study. Upon enrollment, all participants were in the active phase of labor (defined as having 3 - 5 uterine contractions/10 minutes lasting for 30 - 40 seconds and a cervical dilation $\geq$ 3 cm, with vertex presentation). The exclusion criteria were having a Body Mass Index (BMI) of >30 or <20 Kg/m^2, preeclampsia, using psychiatric drugs, opioid or alcohol consumption, occurrence of antenatal hemorrhage, fetal distress and requesting epidural analgesia. After explaining the whole procedure, an informed written consent was obtained from participants, the mothers then were randomly allocated into two groups: 1. Incremental bolus administration of Remifentanil 2. Incremental infusion of Remifentanil. A computerized random number generator was used for sequence generation. Simple randomization with a 1:1 allocation ratio was used in this study. We used the consecutive opaque envelopes for the allocation concealment. The envelopes were opaque when held to the light and opened sequentially and only participant's name and other details were written on the appropriate envelope. In the randomly assigned Remifentanil infusion group, Remifentanil was incrementally infused with the starting dosage of 0.025 μg/kg/min and as required the infusion rate was increased to reach the doses of 0.05, 0.075 and 0.1 μg/kg/min. In the randomly assigned Remifentanil bolus administration group, Remifentanil was given by bolus PCA using an IVAC PCAM model P5000 pump, with the starting dosage of 0.25 μg/kg and as required increased to reach the dose of 0.4 μg/kg with a lock-out time of four minutes. Vital signs (blood pressure, heart rate and respiratory rate) and SPO_2 of the participants were assessed every five minutes, while the fetal heart rate (measured by continuous electronic monitoring) was measured every 15 minutes. The pain intensity of uterine contractions was evaluated based on the Verbal Numeric Rating Scale (VNRS) (ranging from 0 = no pain, to 10 = worst imaginable pain), while the sedation was assessed based on the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale (ranging from 1 - 5). The pain and level of sedation were assessed every 15 minutes. Fetal station and cervical dilation were evaluated by the obstetrician every one hour in the stage I of labor. Fetal station was measured every 15 minutes in the stage II of labor. Remifentanil dosage was increased when VNRS was ≥ 7. Based on the standard protocols, Oxytocin was infused in cases with inappropriate labor progress (12). Remifentanil was discontinued if any of the following criteria were detected: heart rate (HR) <50 beats/min, Systolic Blood Pressure (SBP) <90 mmHg, $SPO_2 <90$ and respiratory rate (RR) <8 breaths/min. The total dosages of administered Oxytocin and Remifentanil were recorded for all participants. In addition, the APGAR scores were assessed at 1 and 5 minutes after birth. SPSS® 15.0 software (SPSS Inc., Chicago, IL, USA) was used for analyzing data. Numerical variables were presented in means and standard deviations (mean ± SD) and categorical variables were presented in numbers and percentages. t-test, paired t-test and ANOVA Test were used. P value <0.05 was considered statistically significant.

4. Results

We assessed two methods of Remifentanil administration (Incremental infusion vs. Incremental Bolus) in two randomly assigned groups of 41 parturient women. There were no statistically significant differences in demographics of the two treatment groups (Table 1). In the Remifentanil infusion group, the pain intensity score before the intervention was 8.95 ± 0.7. After Remifentanil administration, there was a significant decrease in pain intensity score in both stage I (5.2 ± 0.9, $P < 0.001$) and stage II (7.16 ± 0.95, $P < 0.001$) of labor. In the Remifentanil bolus group, the pain intensity score before the intervention was 8.92 ± 0.7. After Remifentanil administration, there was a significant decrease in the pain intensity score in both stage I (5.06 ± 1.11, $P < 0.001$) and stage II (6.98 ± 0.81, $P < 0.001$) of labor. While both methods of Remifentanil administration could significantly decrease the pain intensity scores in stages I and II of labor between the two treatment groups, there were no statistically significant differences between the Remifentanil infusion and bolus groups for pain intensity scores after the intervention in stages I ($P = 0.49$) and II ($P = 0.36$) of labor (Table 2). There were no statistically significant differences between the Remifentanil infusion and bolus groups regarding the duration of stages I and stage II of labor ($P = 0.13$, $P = 0.4$, respectively), the average dosage of Oxytocin administration ($P = 0.8$) and the Sedation Score after Remifentanil administration ($P = 0.89$) (Table 3). However, in the infusion group, the average dosage of Remifentanil administration was significantly lower than the bolus group ($P = 0.001$) (Table 3). Six newborns in the Remifentanil infusion group and five in the Remifentanil bolus group had an APGAR score <7 at one minute after birth. However, all newborns improved with primary care and did not require Naloxone administration. There were no statistically significant differences in newborns APGAR scores

Table 1. Characteristics of Parturient Women in the Remifentanil Infusion and Bolus Groups [a]

Characteristics	Infu. Group	Bolus Group	P Value
Maternal age, y	24.83 ± 4.67	24.83 ± 4.67	0.69 (N.S)
Maternal BMI, Kg/m^2	24.07 ± 2.21	24.07 ± 2.21	0.45 (N.S)
Gestational age, wk	38.61 ± 1.16	38.49 ± 1.23	0.65 (N.S)

[a] Abbreviations: Infu, Remifentanil infusion; Bolus, Remifentanil bolus; SD, Standard Deviation; BMI, Body Mass Index; NS, Non-Significant.

Table 2. Average Visual Analog Scale (AVAS) Pain Scores Before and After Remifentanil Administration in Stages I and II of Labor[a]

Characteristics	Infu Group	Bolus Group	P Value
Pain score at inclusion, time 0	8.95 ± 0.7	8.92 ± 0.7	0.73
Pain score in stage I	5.2 ± 0.9	5.06 ± 1.11	0.49
Intra group P value, stage1 vs. time 0	< 0.001[b]	< 0.001[b]	
pain score In stage II	7.16 ± 0.95	6.98 ± 0.81	0.36
Intra group P value, stage II vs. time 0	< 0.001[b]	< 0.001[b]	

[a] Abbreviations: Infu, Remifentanil infusion; Bolus, Remifentanil bolus.
[b] P Value < 0.05.

Table 3. Dosage of Drugs and Obstetric Data in the Two Groups (n = 41) [a]

Characteristics	Infu. Group	Bolus Group	P Value
Average of Remifentanil dose, μg	639.2 ± 115.2	942.6 ± 86.4	< 0.001
Average of Oxytocin dose, IU	15.8 ± 13.1	15.2 ± 11.8	0.8
Duration of labor, min			
Stage I	165.3 ± 38.7	153.2 ± 34.2	0.13
Stage II, mean ± SD	42.1 ± 12	40 ± 10.3	0.4
Sedation Score after Remifentanil administration	4.8 ± 0.1	4.8 ± 0.1	0.89

[a] Abbreviations: Infu, Remifentanil infusion; Bolus, Remifentanil bolus; μg, Micrograms; SD, Standard Deviation; IU, Internation Unit.

between the two treatment groups (P = 0.9). None of the participants in both groups had SBP < 90 mmHg, SPO_2 < %90, RR < 8 breaths/min and HR <50 beats/min. Nausea and vomiting were observed in three participants in the infusion group and five participants in the bolus group. There were no statistically significant differences between the two groups (P = 0.9). Maternal satisfaction was considerable in the both groups. 95% of the participants in the infusion group and 92% in the bolus group rated analgesia as good to excellent. There was no statistically significant difference between the two groups (P = 0.8).

5. Discussion

In the current study, we compared the efficacy of two methods of Remifentanil administration (incremental infusion vs. incremental bolus) in two groups of 41 parturient women in active phase of labor. Both methods of Remifentanil administration were highly effective in reducing labor pain in stages I and II of labor. There were no statistically significant differences between the two groups for pain intensity, duration of labor, maternal sedation, satisfaction and adverse maternal and neonatal effects. Only the total dosage of administered Remifentanil was significantly different between the two groups, which was lower in the infusion group compared to the bolus group. In our study, Remifentanil infusion at doses of 0.025 - 0.1 μg/kg/min and Remifentanil PCA bolus administration at doses of 0.25 - 0.4 μg/kg with a lock-out time of four minutes were both effective and safe in reducing the labor pain, without marked maternal or neonatal side effects. This was almost consistent with other studies showing that Remifentanil infusion at rates between 0.025 and 0.05 mcg/kg/min combined with rescue Remifentanil PCA bolus at doses of 0.25 - 0.4 mcg/kg could be effective and safe (8-11, 13). In the current study, there was no significant difference in the efficacy of intravenous (IV) infusion versus PCA bolus administration of Remifentanil in reducing the labor pain in parturient women. This was different from other studies that showed a lesser efficacy for IV infusion of Remifentanil compared to the bolus administration. Blair et al. in their study of 21 parturient women compared the analgesic effect of adding a background infusion (0.025 - 0.05 μg/kg/min) to Remifentanil bolus administration with a lockout time of two minutes

(14). They found a significant reduction in pain scores in both groups; however, the authors indicated that adding a background infusion does not reduce pain scores, but serves only to increase respiratory depression and sedation (14). Shen et al. in another study compared the effect of bolus (0.1-0.4 μg/kg with a 2 minutes lock-out) and IV infusion (0.05 - 0.2 μg/kg/min) of Remifentanil administration in 60 parturient women (9). They concluded that Remifentanil PCA bolus reduced labor pain more than continuous infusion. The observed differences might be due to the longer lock-out time we used in our study; we used a lock-out time of four minutes and other studies used a lock-out time of two minutes (9, 14). In this study, Remifentanil administration reduced the pain in both stages I and II of labor. Previous studies reached controversial results regarding the efficacy of Remifentanil in the second stage of labor; some authors declared that Remifentanil only reduces pain in the first stage of labor (11, 14), while others recently suggested that this method might also reduce pain in the second stage of labor as well (10, 15). The use of Remifentanil did not lengthen the duration of first and second stages of labor. In our study, the duration of the first and second stages of labor in parturients who received Remifentanil were 159.28 ± 36.48 minutes (2.6 ± 0.6 hours) and 41.13 ± 11.19 minutes (0.6 ± 0.1 hours), respectively, which were not longer than the expected labor durations based on the Williams textbook (16). This was consistent with other studies indicating that Remifentanil administration does not increase the duration of first and second stages of labor. In the study of Ismail et al. the duration of active phase of the first stage of labor was 1.8 ± 0.6 hours and the duration of the second stage was 0.95 ± 0.4 hours (17). Additionally, in the study of Freeman et al. the duration of second stage of labor was lower in the Remifentanil group (20 minutes) than the epidural analgesia (24 minutes) group (15). In our study, we used lower doses of bolus Remifentanil administration, therefore the duration of labor in the active phase of the first stage of labor was longer than the mentioned studies. Both IV infusion and PCA bolus administration of Remifentanil were safe and not associated with any serious adverse effects in mothers and the neonates. Similar to our study, there were no severe adverse maternal and fetal reactions in both routs of Remifentanil administration in the study of Shen et al. (9). However, in the study of Ismail et al., there were higher rates of maternal and neonatal adverse effects in the Remifentanil group. This might be due to higher doses of Remifentanil used in their study (17). Volikas et al. studied maternal and neonatal adverse effects of Remifentanil in 50 parturient women (18); they concluded that Remifentanil at the PCA bolus dose of 0.5 μg/kg had an acceptable level of maternal adverse effects and minimal effect on the neonate. They indicated that Remifentanil crosses the placenta, but not associated with any adverse fetal or neonatal outcome and it appears to be either rapidly metabolized or redistributed in neonate (18). The strengths of this study were the large sample size compared to other studies and evaluating the effect of IV infusion and PCA bolus administrations of Remifentanil in the second stage of labor, which is not performed in most similar studies. Our study had some limitations; in this study we did not have a control or placebo group. Having a control or placebo group could help us in better interpretation and conclusion of the results, also could help us in eliminating the possibility of placebo effect in this study. Both IV infusion (at the doses of 0.025 - 0.1 μg/kg/min) and PCA bolus (at the doses of 0.25 - 0.4 μg/kg with a lock-out time of 4 minutes) administration of Remifentanil safely and effectively decrease pain in the first and second stages of labor without serious maternal and neonatal adverse effects and without increasing the duration of labor. The average dose of Remifentanil needed to reduce the labor pain was significantly lower in IV infusion method compared to the PCA bolus method. Therefore, we suggest using Remifentanil IV infusion to reduce labor pain in parturient women as an effective and safe labor analgesic.

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