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Original Article

Comparison of remifentanil: Entonox with Entonox alone in labor analgesia

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Abstract

Background: We designed a study to evaluate the effectiveness of continuous low dose infusion of remifentanil adding to self-administration of entonox administered for pain relief during the active phase of first stage of labor.

Materials and Methods: Thirty healthy term pregnant women recruited in our randomized double-blind, cross over study. They received the study medicines during two 30-min periods with a 15-min wash-out sequence after each period. Fifteen parturient used remifentanil as a single bolus dose followed by constant low dose infusion and self-administration of entonox (group R) during the first period and entonox and saline (group P) during the second period, while the remainder of the parturient used the drugs in a reverse order. Pain and Ramsay score, maternal and fetal hemodynamic, and ventilation were assessed during each intervention.

Results: In this study, mean pain severity scores were 8 ± 0.9 before and 5.4 ± 1.7 after intervention in group P, and 7.8 ± 0.1, 3.5 ± 1.3 in group R, respectively. Mean pain severity difference was 2.6 ± 1.5 in group P, while 4.3 ± 1.5 in group R; so, use of entonox and remifentanil can decrease labor pain two times more in comparison with entonox/placebo (normal saline). However, hemodynamic and ventilation parameter in remifentanil/entonox period were same as in entonox/placebo period. No statistical differences were seen in mean Ramsay score between group R and P. There was no episode of maternal bradycardia, hypotension, or hypoxemia.

Conclusion: Not only adding low dose infusion of remifentanil to self-administration of entonox was notable in labor pain reduction, it did n't make more parturient and neonatal side-effects.

Key Words: Entonox, labor pain, remifentanil

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INTRODUCTION

Labor pain is a dynamic process, which is one of the most severe pains that a woman can experience in her life. Several factors have effect on the degree of labor pain, such as psychological preparation, familial emotional support, another labor experiences, and using oxytocin for induction or augmentation of labor; so, vaginal delivery is not preferred more than cesarean section.[1-3]

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Data published in 2005 showed that cesarean section constituted 47% of all deliveries in Iran. On the other hand, many studies showed that normal vaginal delivery has a better outcome for mother and fetus in comparison with cesarean section; so, several options including entonox, different opioids, and epidural analgesia have been used for reduction of labor pain.[2-5] Because of lacking suitable and acceptable analgesic method for women who has contraindicated for epidural analgesia or refused it, it necessitates the other safe method for mother and her fetus.

Entonox is a mixture of 50% nitrous oxide (N_2O) and 50% oxygen. It is an inhalational analgesic agent commonly used as both a sole analgesic and as an adjuvant to systemic and regional analgesic techniques to control labor pain; so, it can be regarded as a standard analgesic method.[1,6,7] Self-administered use of this agent makes it safe and easy for parturient. It also has a quick onset of action and quick recovery time, but it has limited efficacy.[6]

Remifentanil is an ultra-short-acting m-receptor agonist related to fentanyl group. It is rapidly hydrolyzed to an inactive metabolite by red blood cell and tissue esterase. Remifentanil does not accumulate, even after prolonged administration.[8-11] Remifentanil crosses the placenta, but it is eliminated quickly in the fetus by rapid metabolism and redistribution that makes it suitable as a labor analgesic.[10,12]

Experience is limited regarding effectiveness of remifentanil analgesia during labor. We designed a study to evaluate the effectiveness of continuous low dose infusion of remifentanil adding to entonox when it is administered to relieve pain during the active phase of first stage of labor. We hypothesized that remifentanil and entonox would provide better analgesia and fewer side-effects during normal vaginal delivery.

MATERIALS AND METHODS

The study was done in summer of 2011 in ISFAHAN SHAHID BEHESHTI hospital. After approving the Ethic Committee of Isfahan Medical University, 30 healthy term pregnant women who agreed with written informed consent recruited in randomized double-blind, cross over study.

The parturient were eligible for the study, if they have singleton American Society of Anesthesiologists physical status I parturient without any maternal and fetal complications such as pre-eclampsia. Patients were recruited during the active phase of labor when cervical dilatation was about 4-8 cm. The patients who were opium abuser, cigarette smoker or had history of chronic NSAIDS or analgesic drugs use were excluded.

After computerized randomization, the selected parturient received the study medicines during two 30-min periods with a 15-min wash-out sequence between two period. Fifteen parturient used remifentanil (GlaxoSmithKline) and entonox (Darman Gas 50% N_2O 50% oxygen) through a tightly fitting face mask during the first period and entonox and normal saline during the second, while the remainder of the patients used the drugs in a reverse order.

Remifentanil had been used as a single bolus dose of 0.25 μg/kg and then continued with continuous infusion rate of about 0.025 μg/kg/min. Pain scores were assessed using visual analogue scale (VAS) during the intervention.

Patients' heart rate and hemoglobin oxygen saturation (SpO_2), respiratory rate, and fetal heart rate (FHR) were monitored continuously, and systolic, diastolic, and mean arterial pressure were recorded every five min.

The pain was assessed with VAS at the beginning of intervention and then after each contraction. Nausea and sedation score were recorded at the baseline and at the end of each period using VAS and Ramsay score, respectively. Finally, duration of labor active phase was evaluated. APGAR scores were noted at one and five minutes for each case at delivery. All the information were gathered and analyzed by SPSS software version 18.

Data comparisons between two groups were done by Mann-Whitney test for continuous variables and Chi-square test and Fisher's exact test for categorical data. The level of statistical significance was *P* value less than 0.05.

RESULT

Thirty women (19 nulliparous and 11 multiparous) were enrolled in the study. The data concerning the characteristics of the patients are shown summarized in Table 1. There were no statistically significant differences in the demographic data between the two groups.

The pain score before the intervention in parturient who was in group R was 7.8 ± 1 and was 8 ± 0.9 in group P (PV = 0.25), and after drug administration, VAS decreased to 3.5 ± 1.3 and 5.4 ± 1.7 in each group, respectively. There were significant differences between two groups (PV < 0.001).

The mean pain score less than three was seen more in group R (11/30) than in group P (1/30) (91.7% versus 8.3%); on the other hand, in placebo group, pain score higher than six was more than in remifentanil group. The frequency distribution of pain score (3-6) is shown in Figures 1 and 2.

Statistical analysis showed significant differences between two groups.

The range of nausea score was 0-1 for both the groups, and no differences were seen between them. It is notable that only one patient complained of vomiting in remifentanil group.

The parturient gave higher sedation scores during the administration of remifentanil and entonox than during entonox and placebo administration: 2.17 ± 0.59 and 1.87 ± 0.43, respectively, but no differences were seen. No differences were seen between the two groups with respect to systolic, diastolic, and mean arterial blood pressure, heart rate, and respiratory rate before and during the intervention.

During fetal monitoring, no significant changes in FHR were observed between baseline tracings and those recorded after initiating the intervention, and all newborns had APGAR scores of nine and ten at one min, except one, who had APGAR scores of eight at five min, it was nine and ten for all the infants.

Labor active phase duration was 2.6 ± 1.1 hour with the minimum and maximum time about 1.3 and 5.3 hours, respectively. In primipara, the time was 2.77 ± 1.08 and 2.24 ± 1.29 in multipara. One parturient was delivered by cesarean section due to full arrest complication.

Table 1: Characteristics of the parturient

Character	Group A	Group B	*P* value
Age	25.5±5.9	26.3±3.5	0.65
Height	160.6±4.7	162.2±4.7	0.36
Weight	72.5±13.6	69.1±8.7	0.42
BMI	28.2±5.7	26.2±5.7	0.27
Cervix dilatation	4.33±0.62	4.13±0.35	0.29

BMI: Body mass index

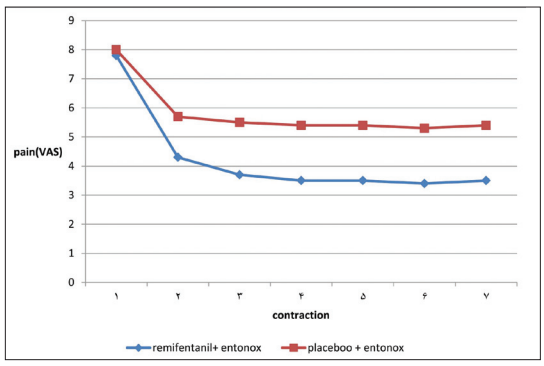

Figure 1: The comparison of pain VAS score in groups R and P

DISCUSSION

In this study, infusion of low dose remifentanil accompanied with self-administered entonox decreased labor pain score significantly. Mean pain score change in individuals who had been prescribed remifentanil with entonox was 4.3 ± 1.5. Other than pain reduction, parturient have benefited from other properties of opioids such as anti-anxiety effect and sedation. Although no differences were seen in mean Ramsay score between group R and P, it was higher in group R, but all of the parturient were responsive to voice.

For many years, different approaches have been used to decrease labor pain such as different kind of opioids, epidural analgesia, entonox inhalation, acupuncture and etc., but not all of them are acceptable by women completely. Furthermore, many women refer to hospital at the end of first phase of labor; so, not all of the mentioned approaches are doable for them.

In previous studies, although women were satisfied with entonox, it cannot decrease pain score effectively in most of them.[13-15] However, most of the patients use entonox on the onset of contraction by self-administration method, but mostly the maximum effect of painlessness do not coincide with the time of maximum pain; so, in order to decrease pain more, Blair *et al.* have administered entonox and pethidine simultaneously, which caused more maternal (SpO_2 reduction) and neonates (APGAR score decrease) complications.[16]

In Volmanen *et al.*'s study, self-administration of entonox and remifentanil were compared with each other. In that study, remifentanil decreased pain score more than entonox, but pain severity was still high

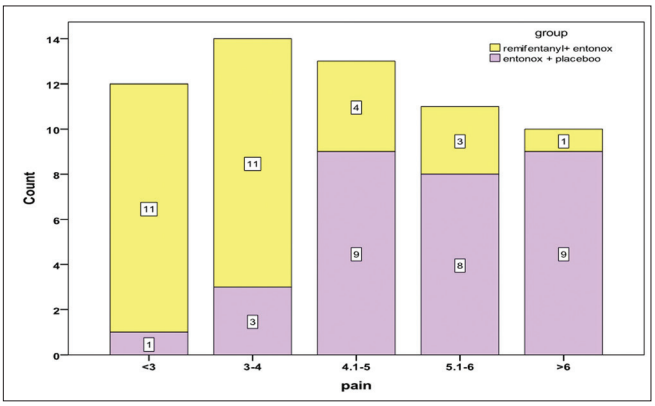

Figure 2: The frequency distribution of pain

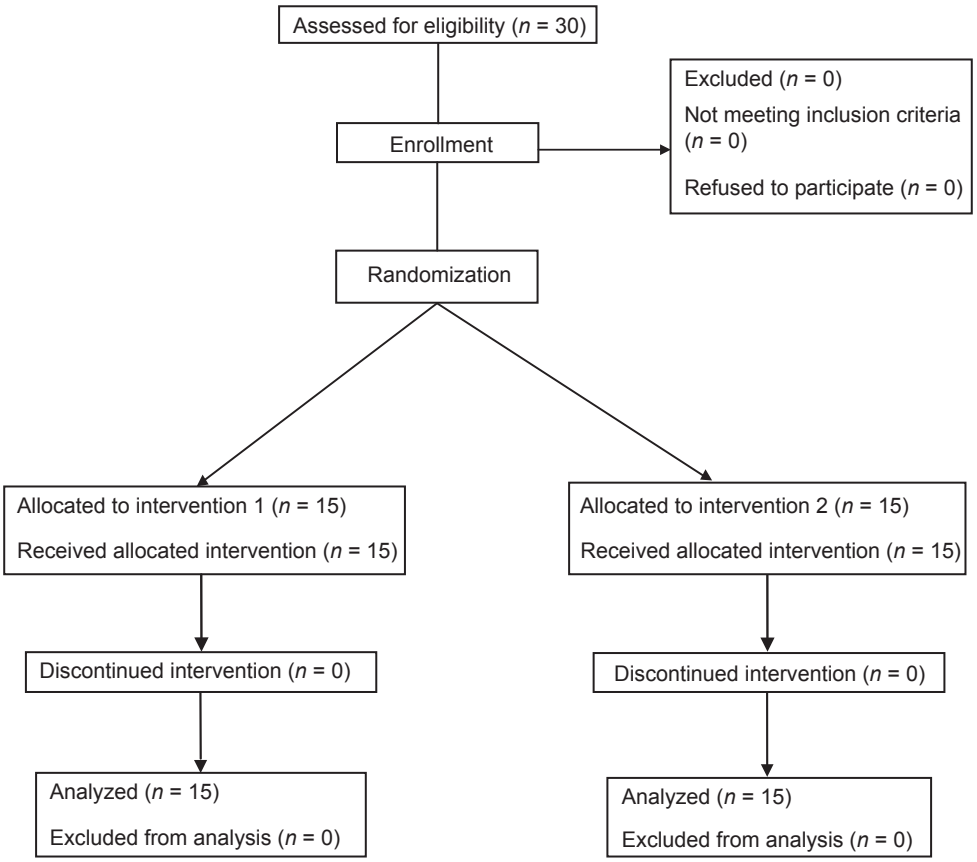

Figure 3: Flow diagram of randomized patients

even with remifentanil administration. The mean of pain score difference in remifentanil group was 1.5 and in entonox group was 0.5.[10]

In our study, continual infusion of low dose of remifentanil (0.025 μg/kg/min) was used in order to have a basic level of pain relief and sedation. When entonox is added to remifentanil, it has more painless effect during contraction so that parturient will have appropriate painlessness during maximum pain.

In this study, mean pain severity in the group P was 8 ± 0.9 before intervention and 5.4 ± 1.7 after intervention. The mean pain severity difference was 2/6 ± 1/5, while the mean pain severity at onset and end of intervention in the group R were 7.8 ± 0.1, 3.5 ± 1.3, respectively, and the mean pain severity changes were 4.3 ± 1.5 in this group; so, use of entonox and remifentanil can decrease labor pain two times more in comparison with entonox/normal saline. There were no episodes of maternal bradycardia, hypotension, or hypoxemia (heart rate < 60 bpm and systolic blood pressure <100 mm Hg, respiratory rate < 8 and SpO2 < 92%, respectively).

Low dosage infusion of remifentanil in comparison to intermittent administration with repeated bolus dosage may decrease the side effects such as lowering level of consciousness, need to reliable airway and insufficient ventilation.

Furthermore, severe pain and anxiety can result in hyperventilation, and it may cause hypocarbia and contraction of uterine vessels that can lead to fetal acidosis and hypoxemia. Basic painless and sedative effect of administering remifentanil with entonox coincidently can prevent from hyperventilation and its mentioned side effects. However, in our study, respiratory rate in remifentanil/entonox receivers was less than in entonox/placebo group, but the least respiratory rate was 12. The results of our study were in agreement with Volmanen *et al.*'s study.[10] Nevertheless, in our study, this drugs combination did not cause hypoventilation or decrease in saturation; the least spo2 was 94%, while in Blair *et al.*'s study, almost 23% of parturient experienced saturation less than 90%.[16]

CONCLUSION

Not only adding remifentanil to entonox with this method was notable in labor pain reduction, it didn' t make more parturient' and neonatal side-effect. In spite of this, multicentric studies in order to prove the

safety of method for common use are recommended.

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