

## Original Article

# Remifentanil for endotracheal intubation in premature infants: A randomized controlled trial

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## ABSTRACT

**Objective:** Endotracheal intubation is a common procedure in neonatal care. The objective of this study was to determine whether the premedication with remifentanil before intubation has analgesic effects in newborn infants.

**Methods:** A total of 40 premature infants who needed endotracheal intubation for intubation-surfactant-extubation method were randomly assigned in two groups of an equal number at two university hospitals. The control group was given 10 µg/kg atropine IV infusions in 1 min and then 2 ml normal saline. In the case group, the atropine was given with the same method and then remifentanil was administered 2 µg/kg IV infusions in 2 min.

**Findings:** For remifentanil and control groups, the mean birth weight were  $1761 \pm 64$  and  $1447 \pm 63$  grams ( $P = 0.29$ ), and the mean gestational ages were  $31.69 \pm 3.5$  and  $30.56 \pm 2.8$  weeks ( $P = 0.28$ ), respectively. Using premature infant pain profile score, infants who received remifentanil felt significantly less pain than the control group ( $15.1 \pm 1.6$  vs.  $7.5 \pm 1.4$ ;  $P < 0.001$ ). There were no significant differences in the duration of endotracheal intubation procedure ( $20.8 \pm 6$  vs.  $22.8 \pm 7.3$  s;  $P = 0.33$ ), the number of attempts for successful intubation and oxygen desaturation between groups.

**Conclusion:** Premedication with remifentanil has good analgesic effects for endotracheal intubation in premature infants without significant derangements in mean blood pressure and oxygen saturation.

**Keywords:** Endotracheal intubation; Remifentanil; premedication; premature infant pain profile score

## INTRODUCTION

Respiratory distress syndrome (RDS) is a common clinical condition that is caused by surfactant deficiency. It is characterized by the early onset of respiratory symptoms such as cyanosis, grunting, retraction, and tachypnea.<sup>[1]</sup> The usage of surfactant either as prophylactic or as a rescue therapy in infants with RDS reduces the chance of air leak syndrome and death.<sup>[2,3]</sup> The administration of surfactant by the method of intubation-surfactant-extubation (INSURE)

was introduced by Victorin *et al.*, in 1990.<sup>[4]</sup> This method needs for endotracheal intubation and laryngoscopy, which causes severe pain in the baby awake and associated with conditions such as drastic changes in the mean blood pressure (MBP), heart rate (HR), and oxygen saturation (SpO<sub>2</sub>).<sup>[5]</sup> According to the International Evidence-Based Group for pain in 2001 tracheal intubation without the use of analgesia or sedation should be performed only for resuscitation in the delivery room or for life-threatening situations associated with the unavailability of intravenous access.<sup>[6]</sup> However, there is no consensus for the drug type and the method of drug administration during endotracheal intubation.<sup>[7,8]</sup> Several drugs have been evaluated for using as the pre-medication for endotracheal intubation. For example, the ant-cholinergic agents including atropine could prevent the occurrence of reflex bradycardia of endotracheal intubation and help to keep the mouth and nasal mucosa dry.<sup>[9,10]</sup> Other categories are benzodiazepines,

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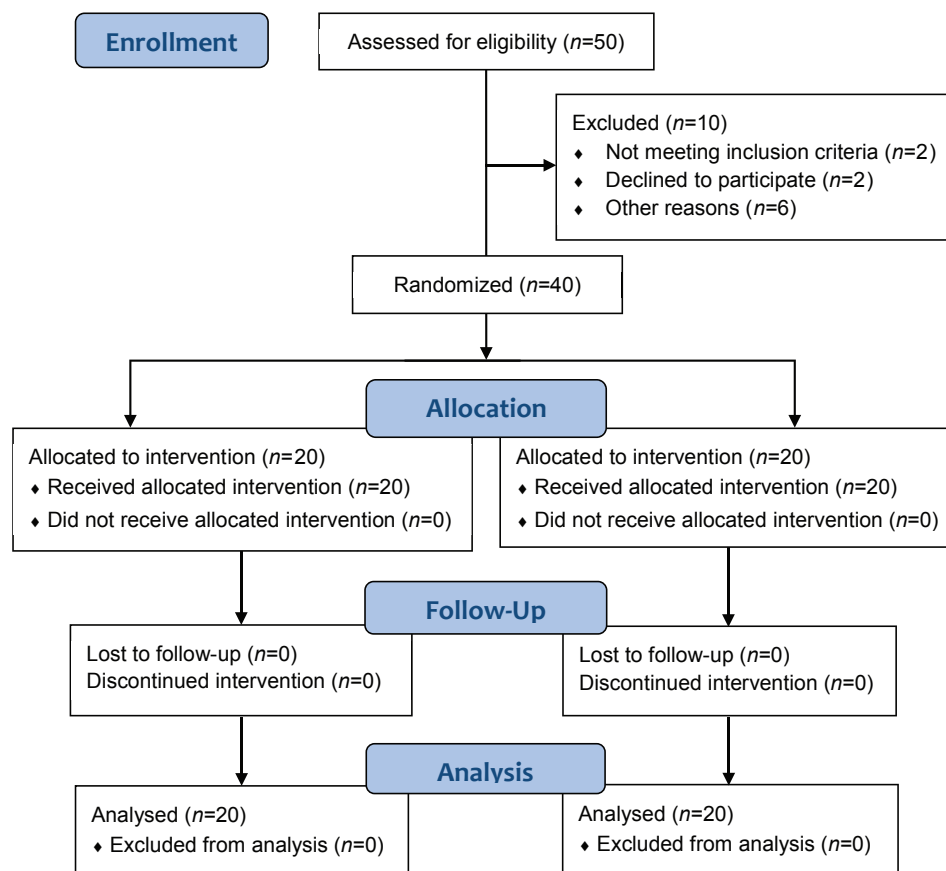
which are in the sedative drugs, and the typical drug is midazolam. Today, they are used less frequently because of the detrimental effects of benzyl alcohol as a pharmaceutical excipients.<sup>[11]</sup> Thiopental is a hypnotic drug, which is usually used in the induction phase of rapid sequence intubation (RSI) and hypotension is its side-effect.<sup>[12]</sup> Short-acting muscle relaxants have also been considered such as succinylcholine, pancuronium, vecuronium, and mivacorium. They are used to create more paralytic stage in RSI with sedatives and analgesics.<sup>[13]</sup> Succinylcholine in combination with atropine and morphine has a good effect in the following cases: Successful endotracheal intubation, reducing the hypoxia, and sustaining hemodynamic stability.<sup>[14]</sup> Pancuronium is a very good vagolytic agent and in combination with atropine is effective in the reduction of the reflex bradycardia, laryngospasm and hypoxia caused by the endotracheal intubation.<sup>[15,16]</sup> Mivacorium was less under consideration due to the release of histamine and the caused laryngospasm.<sup>[15]</sup> Among the analgesic drugs, the drugs of opioid group have many usages, and it can be pointed to fentanyl and morphine. Morphine is a good analgesic drug, and its onset action is 10-15 min and its duration of action is about 30-60 min. However, it can cause hypotension, apnea, and central nervous system (CNS) depression. Fentanyl can cause side effects such as chest rigidity, hypotension, bradycardia, and laryngospasm, which is reversible by naloxone. The onset of action is 1-5 min and the duration of action is about 15-30 min.<sup>[15]</sup> Apart from remifentanil, the clearance of all of the opioids is reduced, and their usage is limited in the neonatal period.<sup>[17]</sup> The onset of action of remifentanil is 0-2 min and its duration of action is about 3-5 min.<sup>[15]</sup> Its elimination is not related to the infant's liver function owing to the lack of hepatic metabolism. Remifentanil metabolism is by non-specific tissue and plasma esterase, which is existed enough in pre-term infants.<sup>[17]</sup> This drug is without accumulative effect and has proper clearance of 90 ml/kg/min in the infants.<sup>[18]</sup> The adverse drug effects such as chest rigidity and laryngospasm is reversible by naloxone and the recommended dose is 1-3 µg/kg within 1 min IV infusion.<sup>[15]</sup> We conducted this study because there is no consensus about the best analgesic for premedication before intubation in premature infants. The purpose of this study was to evaluate the effects of remifentanyl in premature infants undergoing non-urgent endotracheal intubation during the ENSURE method.

## METHODS

This prospective double-blinded randomized control trial was conducted in a 6-month period between

September 2011 and February 2012 in the neonatal intensive care units of Al-Zahra and Shahid Beheshti University Hospitals, Isfahan, Iran. A total of 40 premature infants with gestational age (GA) of 25-37 weeks and postnatal age of less than 48 h were enrolled in the study if they needed surfactant administration. We administered surfactant via endotracheal tube if newborns had moderate to severe respiratory distress due to RDS based on attending neonatologist diagnosis. Respiratory distress was defined by fraction of inspired oxygen (FiO<sub>2</sub>) more than 40% during nasal continuous positive airway pressure (nCPAP) application to reach a SpO<sub>2</sub> of 88-95%.

The Infants with the following conditions were excluded from the study: 5<sup>th</sup> min Apgar score less than 6, congenital heart disease, maxillofacial anomalies, neuromuscular diseases, and clinical syndromes. Infants with 3 or more times of unsuccessful attempts of endotracheal intubation were also excluded. The stages of selection of the infants were given in Figure 1. This study was approved by Isfahan University of Medical Sciences Ethics Committee, and before enrolling the infant into study, written consent was obtained from the parents. The random selection of the patients as case and control groups was based on a selected box number from 1 to 40. Even numbers were allocated to the control group and the odd numbers to the case group. By using a Canon camera (Legria, FS306 E, Japan), which was fixed on a tripod, all of the followings were permanently recorded: SpO<sub>2</sub>, HR, and MBP on Masimo pulse oxymeter (Irvine, CA) at all stages. All stages of implementation, physical states of the infant, the infant's facial expressions during the laryngoscopy and intubation were recorded by mobile shooting with a Sony camera (HDR-XR150 E-Japan) by another person. Video recordings were started before giving medication to the infants up to 5 min after the INSURE. Preparation of the drugs was conducted by a medical expert, so that 10 µg/kg of atropine was prepared for the case and control groups. It was administered intravenously to the infants over 1 min. Then, 2 ml normal saline was injected to the group control and 2 µg/kg of remifentanil (Teva Pharma, Switzerland) was administered to the case group by IV infusion over 2 min. In the case of apnea or SpO<sub>2</sub> decreased to less than 70%, positive pressure ventilation (PPV) was applied using the T-Piece resuscitator (Neopuff Infant Resuscitator; Fisher-Paykel, Auckland, New Zealand). In all infants and prior to intubation, oxygen was given to increase the SpO<sub>2</sub> over 94%. Laryngoscopy was performed using the Riester laryngoscope by a fellowship in neonatology who was unaware about the type of the medication used. Surfactant was administered after ensuring the proper position of



**Figure 1:** CONSORT diagram of the study

endotracheal tube in the appropriate location. With the initiation of effective spontaneous breathing, the endotracheal tube was removed and the infant was placed under the nCPAP. If complications such as chest rigidity or severe and resistant laryngospasm were occurred after infusion of remifentanil, 0.1 mg/kg Naloxan IV was used. If during the endotracheal intubation, the SpO<sub>2</sub> decreased to less than 70% or the HR dropped to less than 20% of the baseline or the duration of endotracheal intubation was increased to more than 30 s, the laryngoscope removed and the PPV was applied. This case was considered as a case of failed intubation. All information of this study was recorded within a pre-designed form. All infants underwent brain ultrasonography during 3 days to 7 days after birth for determining the incidence of intra ventricular hemorrhage.

All steps, which were filmed by two cameras were revised at the same time. For adapting the hemodynamic changes and compliance with the plan process, the information was extracted about the following four stages of the plan and recorded in the relevant forms:

Stage I: Basic information

Stage II: After 1 min, the completion of drugs and before laryngoscopy (post medication)

Stage III: Immediately after tracheal intubation (post intubation)

Stage IV: After 5 min, the intubation procedure was completed or initiation of effective spontaneous respiration (whichever was longer).

Hemodynamic data including MBP, HR, and SpO<sub>2</sub> were recorded in each of the above mentioned stages. The duration of intubation was recorded by using a timer from insertion of the laryngoscope into the mouth until the laryngoscope was removed from the mouth after successful intubation. In the case of requiring the re-intubation, the timing was stopped and for new intubation, the timing was performed again. The difficulty in intubation due to the laryngospasm or the blood found due to the damage to the mucosa of the mouth and throat and the duration of apnea caused by medication was recorded. The pain severity scoring was based on premature infant pain profile (PIPP) form.<sup>[19]</sup> The PIPP assigns points for changes in five parameters during the first 30 s after a painful event: Three for different facial actions (brow bulge, eye squeeze, and nasolabial furrow), 1 for HR and 1 for SpO<sub>2</sub>. The following scores were considered: 0-6 for mild pain, 7-12 for moderate pain, and above 12 for the severe pain.

To obtain a sample size, the following equation was used and 20 patients were allocated in each group, respectively:

$$n = \frac{(Z_1 + Z_2)^2 (2S^2)}{d^2}$$

- Z<sub>1</sub>: Is confidence co-efficient of 0.95, which is 1.96
- Z<sub>2</sub>: Is power co-efficient of test 0.8, which is 0.84
- S: Is an estimation of standard deviation of each variable involving consumed time for intubation,<sup>[14]</sup> MBP, HR and saturation of peripheral oxygen
- d: Is minimum average difference of each of the above-mentioned variables between two groups, which makes difference significant and is considered as 0.9S.

Parametric data were analyzed using the Students *t*-test and non-parametric data were analyzed with the Mann-Whitney U-test. In order to investigate the follow-up of quantitative variables from a normal distribution, Kolmogorov-Smirnov test was performed and categorical data were compared by Fisher exact test.

Statistical analysis was performed using the SPSS software version 18.0 (Chicago, Illinois, USA) and *P* value of less than 0.05 was considered as statistically significant.

## RESULTS

A total of 40 premature infants with a GA of 25-37 weeks were randomized, 20 to each study group. Infants in both group had similar demographic characteristics [Table 1]. The hemodynamic data of MBP, HR, and SpO<sub>2</sub> in four stages are shown in Figures 2-4 with the confidence interval of 95%.

A total of 16 infants had apnea following remifentanil administration. The mean duration of apnea was 8.7 ± 5.2 min. The maximum apnea time was 17 min.

As presented in Table 2, there were clear differences between two groups only in scoring pain severity PIPP and it indicated the appropriate and acceptable analgesic effect of remifentanil. In patients who received remifentanil, 4 cases of the chest wall rigidity and 6 cases of laryngospasm were seen. All newborns who suffered from the chest wall rigidity had GAs of less than 32 weeks. Table 3 demonstrates the effects of remifentanil in two subgroups of GAs.

## DISCUSSION

This study aimed to find a way to reduce the pain and other complications of endotracheal intubation in pre-term newborns. We found that the use of

**Table 1: Baseline characteristics of participants**

Characteristics	Remifentanil group (n=20)	Control group (n=20)	P value
Birth weight (g)	1447 (630)	1761 (647)	0.29
Gestational age (weeks)	30.56 (2.8)	31.69 (3.5)	0.28
Sex (male/female)	14/6	11/9	0.25
Baseline heart rate (beat/min)	147.2 (16.3)	147.6 (18.5)	0.95
Baseline mean blood pressure (mmHg)	40.3 (7.3)	41.6 (7.8)	0.59
Baseline SpO <sub>2</sub>	94.3 (5)	94.5 (3.4)	0.85

Data are presented as mean (SD); SpO<sub>2</sub>=Oxygen saturation

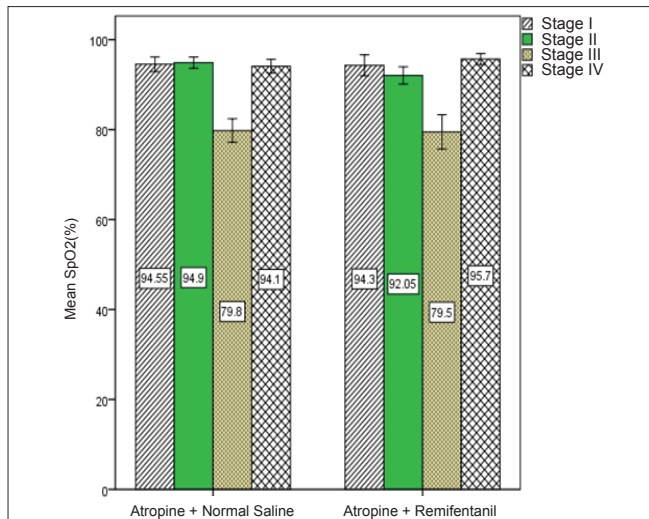
**Table 2: Comparison of clinical parameters between two groups**

Parameter	Atropine, normal saline (n=20)	Atropine, remifentanil (n=20)	P
Mean (SD) duration of successful intubation (s)	22.8 (7.3)	20.8 (6)	0.338
Attempts for successful intubation			
One time	16 (80)	17 (85)	0.667
Two times	4 (20)	3 (15)	
SpO <sub>2</sub> <70 mmHg during intubation	1 (5)	4 (20)	0.171
HR <20% increase of baseline during intubation (beat/min)	1 (5)	1 (5)	1.000
Unsuccessful intubation (duration >30 seconds)	4 (20)	2 (10)	0.331
Mouth and laryngeal bleeding	3 (15)	3 (15)	1.000
Intraventricular hemorrhage	1 (5)	1 (5)	1.000
PIPP score	15.1 (1.6)	7.5 (1.4)	<0.001
Severity of pain based on PIPP score			
Mild (0-6)	0 (0)	4 (20)	<0.001
Moderate (7-12)	1 (5)	16 (80)	
Severe (over 12)	19 (95)	0 (0)	

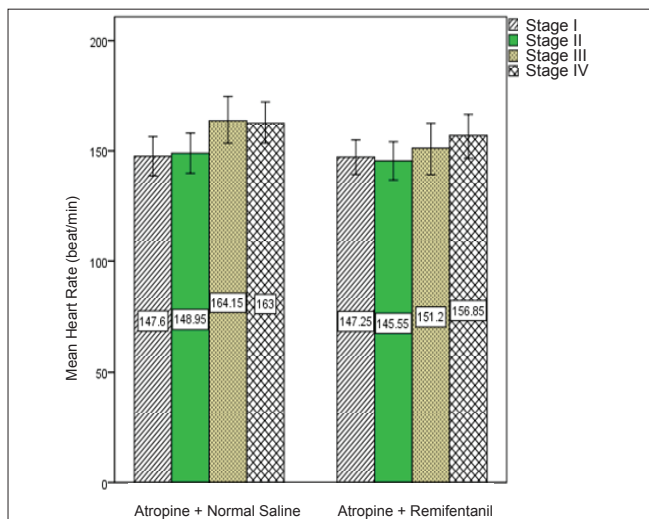
Data are presented as number (%), otherwise specified; SpO<sub>2</sub>=Oxygen saturation, HR=Heart rate, PIPP=Premature infant pain profile

remifentanil caused a significant decrease in PIPP score in pre-term infants during endotracheal intubation. Complications such as chest rigidity and laryngospasm were uncommon especially in infants with GA of more than 32 weeks. However, remifentanil could not reduce the duration of endotracheal intubation.

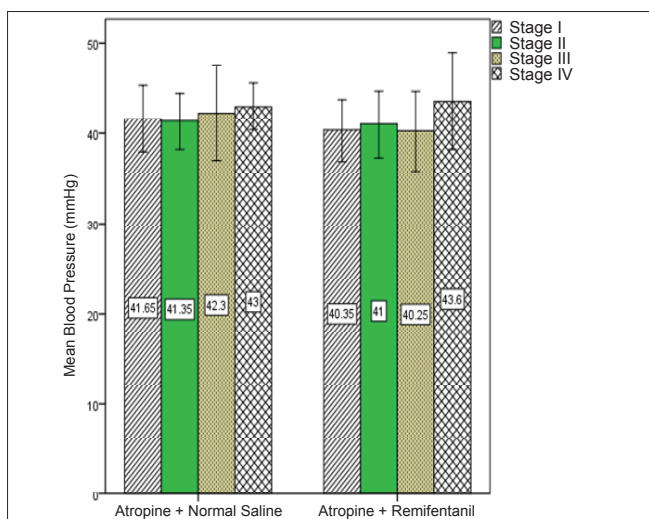
Many studies on different groups of drugs have been conducted to provide the analgesic effect as premedication with minimal side-effects for endotracheal intubation in infants. The result is still not clear. For example, Bhutada *et al.*, conducted a random and non-blinded trial to compare thiopental with



**Figure 2:** Mean (95%CI) of SpO<sub>2</sub> in two groups (SpO<sub>2</sub>: Oxygen saturation)



**Figure 3:** Mean (95% CI) of heart rate in two groups



**Figure 4:** Mean (95% CI) of blood pressure in two groups

**Table 3: Effects of remifentanyl in two subgroups of gestational ages**

Parameter	GA≥32 weeks (n=7)	GA<32 weeks (n=16)	P
Mean (SD) duration of successful intubation (s)	24.1 (4.6)	14.5 (6)	0.87
Attempts for successful intubation			
One time	6 (85.7)	11 (68.8)	0.383
Two times	1 (14.3)	2 (12.5)	0.684
Three times	0 (0)	1 (6.3)	0.696
Four times	0 (0)	2 (12.5)	0.474
Duration of apnea (min)	10 (4.6)	9 (5.2)	0.667
Chest rigidity	0 (0)	4 (25)	0.204
Laryngospasm	2 (28.6)	7 (43.8)	0.418
Naloxan usage	0 (0)	5 (31.3)	0.130

Data are presented as number (%), Otherwise specified; GA=Gestational age

placebo for facilitating the intubation in 30 term infants with mean birth weight of 3270 g. They demonstrated that the duration of intubation, clearly decreased in the thiopental group. During intubation, HR increased in thiopental group, but this increase was lower than the controls. Furthermore, in the thiopental group, MBP had less significant increase compared to the control group. Returning the hemodynamic conditions to baseline levels was faster in the thiopental group. This study has confirmed the protective effect of thiopental on the increase in HR and the blood pressure during intubation. Nonetheless, it did not provide any information regarding the degree of pain or the infants' comfort during the intubation.<sup>[20]</sup> Our study showed that remifentanyl had no significant effect in reducing the duration of intubation. We used atropine in both groups and the appropriate hemodynamic stability may be related to the preventive effects of atropine. In a study conducted by Oei *et al.*, on 20 term and pre-term infants, premedication with atropine, morphin, and suxamethonium in order to facilitate the intubation was compared to awake intubation. They concluded that the use of premedication could reduce the total duration of endotracheal intubation, the number of attempts for successful intubation and iatrogenic trauma even in infants with lesser postnatal age, birth weight, and GA. There were no significant differences between the groups in terms of reducing HR and SpO<sub>2</sub> during intubation.<sup>[21]</sup> However, due to the usage of a combination of several drug categories, the specific effect of each drug on intubation was not clear and the amount of pain relief and the infant comfort was not known. It could be concluded that the use of suxamethonium in this study was effective on reducing intubation time and number of attempts for successful intubation. In another comparative randomized study by Lemyre *et al.*, the effect of morphine as a pre-medication for nasotracheal

intubation was investigated on 34 premature infants. It was concluded that in the two comparing groups, the duration of severe hypoxia, intubation duration, number of attempts for successful intubation, and increased the blood pressure were identical. Bradycardia were seen in 94% of all of infants and the median duration of intubation in the study group was 3 times longer than the control group despite no statistical differences.<sup>[22]</sup> In this study, intubation performed 5 min after the injection of morphine which is very soon because the onset of action of morphine is 15-30 min. So it might cause error in the appropriate conclusions. In a comparative study performed by Roberts *et al.*, 41 term and pre-term infants were allocated in two groups of fentanyl/atropine and fentanyl/atropine/mivacurium. Both groups were compared in terms of amount and duration of hypoxia in four thresholds of 85%, 75%, 60%, and 40%, total time of intubation, total time of laryngoscopy, and the number of attempts for successful intubation. It was concluded that in mivacurium group, the SpO<sub>2</sub> of less than 60% with any length of time was obviously lower. Total procedure time was 3 times lower and total laryngoscopy time was 2 times lower in mivacurium group. There was no difference between the two groups in terms of changes in HR and MBP. They suggested to add a short-acting muscle relaxant (such as mivacurium) to the premedication regimen in all cases of non-emergent endotracheal intubation.<sup>[23]</sup> Possibly, the lack of significant difference in duration of intubation and the frequency of successful intubation (twice or less), in our study, was remifentanil consumption alone and without the use of a short acting muscle relaxant.

Crawford *et al.*, performed a two stage study. Initially, they showed that the effective dose of remifentanil in 98% of infants is  $2.8 \pm 0.5 \mu\text{g}/\text{kg}$ . In the second study they randomized 24 infants to receive either propofol/remifentanil or propofol/succinylcholine to facilitate endotracheal intubation.<sup>[24]</sup> They evaluated the criteria for good clinical research practice (GCRP)<sup>[25]</sup> that had five portions including jaw relaxation, ease of laryngoscopy, position of the vocal cords, coughing and the intensity and strength of limb movement. They demonstrated that the duration of apnea and intubation conditions did not significantly differ between groups. No severe adverse effects such as bradycardia, hypotension or chest wall rigidity was observed. In remifentanil group, the mean duration of apnea was  $4.3 \pm 1$  min and the mean time for tracheal intubation was  $15 \pm 3$  s.<sup>[24]</sup> Although they used  $3 \mu\text{g}/\text{kg}$  of remifentanil, which is greater than remifentanil dose in our study the mean duration of apnea is about 2 times lower than our study. The mean duration of intubation in our study was longer

than mentioned study, which could be due to lack of use of propofol as an anesthetic drug in our study.

Silva *et al.*, conducted a randomized double-blind study on 20 infants of 28-34 weeks gestation who required intubation because of respiratory failure due to severe RDS. Morphine and midazolam were instructed for the first group and remifentanil ( $1 \mu\text{g}/\text{kg}$ ) and midazolam were given to the other group. They evaluated intubation condition with GCRP criteria and the amount of stress and pain before and after the intubation with the comfort score and the neonatal infant pain scale (NIPS). In the morphine group, none of them had excellent intubation condition in terms of GCRP and 40% of the infants needed for the second attempt intubation. In contrast, the GCRP in remifentanil group were excellent in 60% of the infants. They did not found significant differences between groups with regard to hemodynamic variables including HR, MBP and SpO<sub>2</sub>. Stress and pain, based on the comfort score and NIPS criteria were similar in both groups.<sup>[26]</sup> Chest wall rigidity did not occur in any newborn. We did not use midazolam due to the limitation of consumption of midazolam in preterm infants.<sup>[11]</sup> However, we speculated that midazolam could decrease the incidence of the chest wall rigidity. We used PIPP score for assessment of pain in preterm infants and we also found that remifentanil have good analgesic effects as a premedication for endotracheal intubation. A randomized double blind trial was performed by Choong *et al.*, Newborns in the intervention group received remifentanil ( $3 \mu\text{g}/\text{kg}$ ) and normal saline. The control group received atropine, fentanyl and succinylcholine. It was seen that the success rate of the first intubation attempt was 60% in the remifentanil group and 40% in the fentanyl group, which was not statistically significant. The duration of intubation and the return time of spontaneous respiration were not statistically different between groups. Two cases of the remifentanil suffered from chest rigidity. Intubators were reported favorable intubation conditions in 53.3% and 6.7% in the remifentanil and fentanyl groups, respectively. There was no difference between the two groups in terms of hemodynamic variables and hypoxia. They reported that muscle rigidity is a potential risk with remifentanil at doses of  $3 \mu\text{g}/\text{kg}$ . It was concluded that more studies are needed to determine the ideal dosing regimens and combination of agents for use with remifentanil in newborn infants.<sup>[27]</sup> The ease of intubation and lack of chest rigidity in fentanyl group could be attributed to the use of succinylcholine in this group. Although in our study, the remifentanil dose was lower and the injection time was longer than the mentioned study, but laryngospasm and the chest rigidity had been more obvious in our plan. In addition, the return time of

effective spontaneous respiration in our study had been longer. In the only specific study on remifentanil as a pre-medication before INSURE by Welzing *et al.*, as a pilot study, 21 pre-term infants with GA of 29-32 weeks underwent the intubation by different persons with different experience levels. Remifentanil (2 µg/kg) was injected over 1 min after receiving 10 µg/kg atropine. In order to assess intubation condition, an innovative approach was used with regard to the incidence of limb movement, coughing or retching and breathing. They reported the successful intubation rate of 71% in the first attempt and 29% in the second attempt. Two cases of failed intubation were due to performing the intubation by inexperienced people and not due to lack of good drug effect. Nearly, 67% of the infants had excellent intubation condition and 33% were in good condition. There were no drastic changes in the HR, BP, SpO<sub>2</sub>, and only one case was needed the injection of saline due to the hypotension. None of the cases had chest rigidity and the total average time of INSURE from the remifentanil infusion up to the end of the procedure was 5 min.<sup>[28]</sup>

Although our sample size was small and we did not assess intubation condition, our study has some important powers. First of all, our research was a comparative double-blind study. Secondly, only one person performed all the intubations to avoid the risk of bias due to a different level of experience of intubators. Thirdly, this was the first time that the PIPP index was used for assessment of pain during endotracheal intubation. On the other hand, this study following the study of Welzing *et al.*, was the second study, which was designed for premedication for ENSURE method.

In conclusion, the administration of 2 µg/kg remifentanil as premedication for endotracheal intubation in premature infants provided stable hemodynamics and good analgesic effects. However, it seems that remifentanil could not reduce the duration of endotracheal intubation. Moreover, chest wall rigidity is a complication of remifentanil administration. Therefore, it is necessary to conduct more studies using other complementary drugs such as muscle relaxants, for shortening the time of intubation and reducing the possibility of the chest wall rigidity. Actually, it can be recommended that until performing future trials with larger sample sizes, remifentanil should be used with caution on a dose of 2 µg/kg as premedication for endotracheal intubation especially, in more preterm infants.

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## AUTHORS' CONTRIBUTION

Z. Badiee made substantial contribution to data base research, proposal preparation, writing and revising the manuscript. M. Vakiliamini contributed to data collection, randomization and manuscript preparation. M. Mohammadzadeh contributed in proposal and manuscript preparation.

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