IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Original Article

Comparison of the Effect of Remifentanil Plus Atropine with Fentanyl and Remifentanil Alone on Preterm Infants' Vital Signs in Non-emergency Intratracheal Intubation

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ABSTRACT

Background: Intratracheal intubation is associated with many side effects. Different groups of drugs have been used to control these side effects, but there is still no consensus on the most suitable drugs.
This study aimed to compare the effect and possible side effects of fentanyl, remifentanil, and atropine plus remifentanil on the vital signs of preterm infants in non-emergency intratracheal intubation.
Methods: In this randomized clinical trial study, 75 neonates with a gestational age of 27 to 34 weeks who required temporary intubation were included in the study and divided into three groups by computer randomization. Then, the effects and possible side effects of remifentanil, fentanyl, and remifentanil with atropine on clinical parameters (blood pressure, heart rate, and arterial oxygen saturation) were investigated.
Results: A total of 75 neonates with a mean gestational age of 30.4 weeks were studied. There was no significant difference between study groups in terms of changes in the systemic blood pressure and heart rate, but the mean oxygen saturation in all three groups was significantly different at different measurement times (P-value: 0.036). The group receiving remifentanil plus atropine reported minimal changes in oxygen saturation and their oxygen saturation was significantly higher than the other groups 30 min after extubation.
Conclusion: The use of remifentanil with atropine in preterm infants is associated with lower changes in oxygen saturation and higher arterial oxygen saturation 30 min after extubation. The use of remifentanil or remifentanil with atropine or fentanyl has no significant effect on the blood pressure and heart rate of neonates in non-emergency intratracheal intubation.

Keywords: Atropine, Endotracheal intubation, Fentanyl, Premature infant, Remifentanil

Introduction

Intratracheal intubation is a painful procedure often performed in neonatal intensive care units (NICU). Indications of endotracheal intubation include cardiopulmonary resuscitation, airway management, and the need for intratracheal administration of surfactant, among other things. The most common cause of intubation in neonates is a surfactant replacement therapy for Respiratory Distress Syndrome (RDS), which is currently carried out by the INSURE (Intubation, Surfactant, Extubation) procedure. The rapid return of respiratory activity is essential for a successful INSURE procedure to remove the implanted endotracheal tube soon after surfactant administration. Therefore, the drug used as an analgesic and sedative before intubation should have a very short duration of action (1-2).

Intubation is conducted based on the patient's

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Please cite this paper as:
Mousavi M, Ghojazadeh M, Dadekhani S. Comparison of the Effect of Remifentanil Plus Atropine with Fentanyl and Remifentanil Alone on Preterm Infants' Vital Signs in Non-emergency Intratracheal Intubation. Iranian Journal of Neonatology. 2022 Oct: 13(4). DOI: 10.22038/ijn.2022.64315.2242

condition and whether the intubation is emergent or not. In emergency and life-threatening conditions, patients do not have time to relax and control pain by premedication, and intubation must be performed while they are awake. Wake intubation may increase intubation time and the frequency of intubation attempts, leading to complications such as damage to the face, eyes, tongue, gums, and glottis, as well as changes in vital signs (3). Another side effect of intubation is bradycardia. The use of a laryngoscope in endotracheal intubation may cause apnea, bradycardia, and hypoxemia due to the autonomic reflex. Some studies have shown that atropine may help reduce bradyarrhythmias and conduction disorders due to its anticholinergic effect (4).

Another major complication of tracheal intubation in infants is pain, which mostly affects premature infants, and may result in long-term adverse outcomes, especially in brain development. Many studies explored the effectiveness of premedication in intubation and its effects on the natural physiology and mitigation of adverse physiological responses and complications of intubation. (5-7)

Pain relief is a moral obligation for neonate care, and all neonates need to receive analgesia before endotracheal intubation except in emergencies. The need for premedication before neonatal intubation is well documented and several studies have investigated various drugs in neonatal intubation, but there is still no consensus on the most effective drug for pain relief and physiological instability to ensure suitable conditions without any side effects (8-11).

This study looks into the effects and possible side effects of using remifentanil, fentanyl, and remifentanil plus atropine on neonates' vital signs such as heart rate, blood pressure, and oxygen saturation in non-emergent endotracheal intubation.

Methods

In this blind randomized clinical trial of Phase 3, the participants were selected using the census sampling method from Tabriz Children's and Al Zahra's educational hospitals for 12 months from 2020. Accordingly, seventy-five neonates who were admitted to the NICU and required intubation for the INSUR were included in the study and divided into three groups by computer randomization and Randlist 2.1 software. Inclusion criteria were neonates with a gestational age of 27 to 34 weeks with respiratory distress syndrome requiring intubation for the INSURE. The exclusion criteria were congenital anomalies, perinatal asphyxia, parental dissatisfaction, no extubation after INSURE and cyanotic heart diseases.

To determine the sample size, the results of the pilot study were used for each group. In this study, oxygen saturation was the primary outcome variable. Hence, considering a maximum first-type error of 0.05, the test power of 80%, and a difference of 15% between the groups, a sample size of n=22 was determined and a total of 75 samples were studied.

Research Procedure

First, a checklist was prepared and the information on study neonates and variables such as gestational age at birth, neonate age at the time of the study, and weight were recorded. Then, 75 neonates were divided into three groups (25 neonates in each group) by computerized randomization. They received the following medication protocols and were intubated after 2 min.

Group A: Intravenous fentanyl 2 µg/kg
Group B: Intravenous remifentanil 1 µg/kg
Group C: Atropine 20 µg /kg by slow intravenous injection and 1 min later Remifentanil1 µg/kg intravenously

The neonates in the study were monitored by the Vectra patient monitoring system during the study periods. Before intubation, immediately after extubation and every 10 min, oxygen saturation, heart rate, and neonatal blood pressure were recorded for up to 1 h. Before intubation, pre-oxygenation and positive pressure ventilation were applied to all infants with T-Piece to achieve oxygen saturation above 95%. The inspiratory pressure was determined based on weight, proper chest movement and the disease process. After preoxygenation, drugs were injected in different groups intravenously for 1 min, and intubation was performed 2 min after drug injection. Surfactant was injected after confirming the proper location of the endotracheal tube. Then, after ensuring effective spontaneous respiration, the neonates were extubated and received respiratory support for at least 4 h with the N-CPAP (Nasal-Continues Positive Airway Pressure) made by Fisher Paykel, typically with positive expiratory pressure (PEEP) of 5-6 cmH2O. In all groups, at least two days after the administration of the drugs, the neonates were constantly monitored at the NICU for possible drugs side effects

including respiratory depression, hypotension and bradycardia, respiratory muscle stiffness, impaired lung expansion, urinary retention, vomiting, seizures, arrhythmias, and allergic reactions. In previous articles, the dose of fentanyl and remifentanil of neonates was reported 1-3 µg /kg, but according to a previous study conducted in the researcher's center by Hosseini et al (1), the initial dose of remifentanil was set at 1 µg / kg. They found that using 2 µg/kg of remifentanil is associated with a substantial decrease in oxygen saturation. The drugs were prepared in syringes of the same color by a nurse who was not blind to the study. After receiving the medicine, the pediatrician, blind to the type of injected drugs, intubated the infants. To control bias, none of the people involved in the project were aware of the type of medication for the neonates, except the analytical specialist.

Statistical Analysis

The data was analyzed using descriptive statistical methods (mean/standard deviation and frequency-percentage) and the ratio comparison for the studied groups. The Shapiro-Wilk test was utilized to check the normality of the quantitative variables in the study groups. The ANOVA test was also run for quantitative data with normal distribution in the study groups and the Kruskal-Wallis test was used for the quantitative data with non-normal distribution. The Levine test was used to examine the homogeneity of variances. The Chi-square test and Fisher's exact test were also used for qualitative variables in the groups. In this study, P-value<0.05 was considered significant.

The present study was approved by the ethics committee of Tabriz University of Medical Sciences (code IR.TBZMED.REC.1398.793). In this research, no cost was imposed on the patients and their information was kept confidential. Also, an informed consent form was obtained from the neonates' parents. The present study was registered in the clinical trial registration system (code: IRCT20160102025811N3)).

Results

In this study, 75 neonates were examined. The mean gestational age of the patients was 30.4 weeks and the minimum and maximum gestational ages were 26 and 43 weeks, respectively. The mean weight of patients was 1497 ± 253 g(in the range of 795 g to 3100 g) (Table 1).

Table 1. Comparison of gestational age and weight between the study groups

Drug Type			Gestational age(day)	Weight(gram)
Remifentanil	Mean		218.2800	1540.6000
	Median		213.0000	1400.0000
	SD		25.81911	533.48563
	Minimum		182.00	885.00
	Maximum		301.00	2920.00
	Percentiles	25	205.5000	1052.5000
		50	213.0000	1400.0000
		75	234.5000	1995.0000
Remifentanil+ Atropine	Mean		211.1200	1304.0000
	Median		208.0000	1200.0000
	SD		12.57418	373.66708
	Minimum		182.00	795.00
	Maximum		238.00	2400.00
	Percentiles	25	202.5000	1000.0000
		50	208.0000	1200.0000
		75	220.5000	1550.0000
Fentanyl	Mean		219.4400	1648.4000
	Median		221.0000	1510.0000
	Std. Deviation		20.66414	622.18988
	Minimum		179.00	800.00
	Maximum		258.00	3100.00
	Percentiles	25	205.0000	1110.0000
		50	221.0000	1510.0000
		75	235.0000	2015.0000
P value(Kruskal-Wallis Test)			0.191	0.108

Systemic blood pressure change

The blood pressure of different groups at the beginning of the study is presented in Table 2. As can be seen, there is no statistically significant difference between groups in blood pressure (P-value: 0.109). Findings of changes in the systemic blood pressure of the neonates in study groups and the desired time are shown in Figure 1. As displayed in this diagram, changes in blood pressure in the fentanyl group are almost identical to the atropine plus remifentanil group, but in the latter, the neonatal blood pressure demonstrated a more stable trend at different studied times, though the differences were statistically significant (P-value: 0.109).

Percentage of oxygen saturation

Changes in the percentage of oxygen saturation in the studied groups at the desired times are shown in Figure 2. As can be seen, there is no significant change in oxygen saturation in the remifentanil plus atropine groups. However, the fentanyl group saw a drop in oxygen saturation immediately after intubation in the remifentanil group, where this reduction is more pronounced. Also, 30 min after extubation, oxygen saturation was higher in the remifentanil plus atropine group than in others, but after 1 h, oxygen saturation increased in the fentanyl group (Figure 2). The post hoc tests were used to study and compare changes between different times and groups, the results of which are revealed in Table 3. There is also a significant difference between remifentanil alone and remifentanil plus atropine groups in oxygen saturation. However, compared to the other two groups, there is no significant difference in oxygen saturation.

Percentage of heart rate changes

Table 2 reports the results of heart rate at the baseline between different groups. As can be seen, there is, no statistically significant difference between different study groups in heart rate (P-value: 0.739).

Figure 3 shows changes in the heart rate of patients at the desired times. During the

Table 2. Comparison of blood pressure/oxygen saturation/heart rate at the baseline between different groups

		Mean	SD	Minimum	Maximum	P-value (One-Way ANOVA)
Systemic blood pressure	Remifentanil	43.24	8.95	27.00	61.00	0.109
	Remifentanil+ Atropine	50.32	15.43	30.00	96.00	
	Fentanyl	45.40	10.64	24.00	63.00	
Percent of Oxygen Saturation	Remifentanil	93.24	4.55	82.00	100.00	0.175
	Remifentanil+ Atropine	95.16	3.11	85.00	99.00	
	Fentanyl	94.20	2.85	88.00	98.00	
Heart rate	Remifentanil	146.12	15.56	116.00	181.00	0.739
	Remifentanil+ Atropine	146.96	17.716	116.00	174.00	
	Fentanyl	149.72	17.88	115.00	201.00	

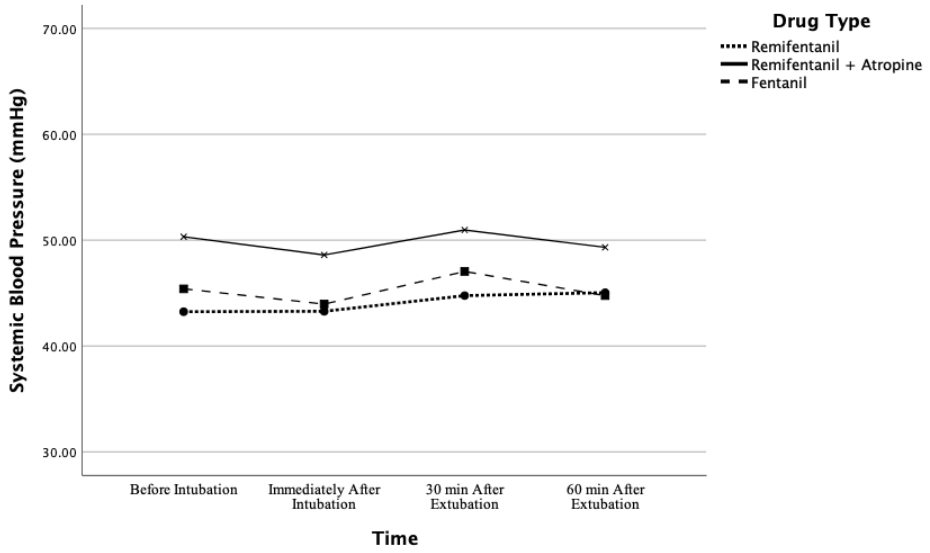

Figure 1. Changes in blood pressure during the study between the three groups

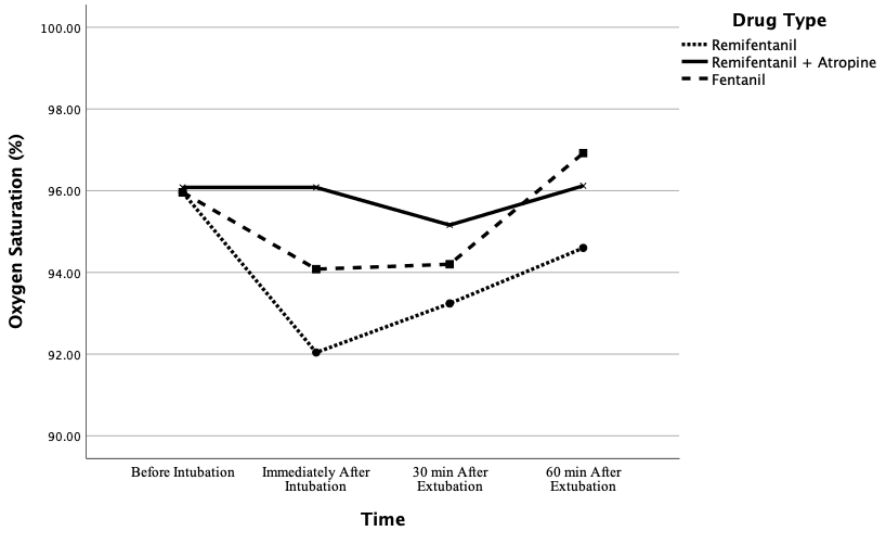

Figure 2. Trend of changes in oxygen saturation of tree groups during the study

Table 3. Post-hoc test comparing oxygen saturation changes in the study groups

Dug	Drug	Mean difference	standard error	p-value
Remifentanil	Remifentanil + Atropine	-1.900	./738	0.012
Remifentanil	Fentanyl	-1.330	./738	0.076
Fentanyl	Remifentanil + Atropine	-0.670	./738	0.443

intubation process, the remifentanil and atropine groups as well as the remifentanil alone group saw an increase in the heart rate, but this change disappeared after the extubation. In the fentanyl group, during the intubation process, there was no considerable change in the heart rate and after the extubation, the heart rate dropped slightly half an hour later. In the remifentanil and atropine groups, the heart rate was higher than the baseline.

Discussion

The application of premedication for non-emergency intubations is preferred at any age because endotracheal intubation is a painful process that can trigger complications such as hypoxemia, bradycardia, and hypertension, which are in turn associated with more severe complications such as intracranial hemorrhage in premature infants. Different studies have reported that the use of analgesic drugs before intubation can improve the results (12-17).

Fentanyl and remifentanil are among the analgesic drugs used in the NICU, with the latter being twice as potent as the former In different studies, the effect of each drug alone or in comparison with other drugs has been investigated and divergent results have been reported (18).

In this study, we tested fentanyl and remifentanil in combination with atropine. Our study showed that the mean oxygen saturation at different studied times in each of these drugs was different and their differences were significant. Also, the mean oxygen saturation in different drug groups was significantly different. However, one hour after the extubation, the oxygen saturation level in the fentanyl group was higher than in the remifentanil group and the remifentanil plus atropine group. However, in the remifentanil plus atropine groups, the changes in blood pressure were small and 30 min after the extubation, higher oxygen saturation was shown. The examination of the blood oxygen saturation chart in the studied patients shows that in patients receiving remifentanil, oxygen saturation first dropped and then increased. However, in patients receiving fentanyl, there was no reduction in oxygenation after the intubation, which may be due to the higher potency of remifentanil compared to fentanyl.

The findings of this study are consistent with those reported by K Choong et al, comparing the effects of atropine with fentanyl and remifentanil on reducing abnormal physiological responses in neonatal intubation. They concluded that the effect of remifentanil on mitigating the physiological side effects during neonatal intubation is similar to that of fentanyl, but remifentanil produces a more favorable effect,

with chest wall stiffness being more noticeable in remifentanil, though the difference is not significant. In our study, no chest stiffness was observed, which could be due to the use of low doses of remifentanil because muscle stiffness can be seen at doses above 1 µg/kg or infusion above 0.1 µg / kg/min. (17-18).

Our study is also consistent with the findings of Bhutada et al. (19) and Clément Chollat et al, who reported a significant effect on pain relief and alleviated complications of intubation in infants receiving a combination of atropine and remifentanil (20). Nevertheless, a study by Badiee et al. on the effect of atropine compared to remifentanil on reducing pain and changes in arterial oxygen demonstrated no significant difference between the two drugs (21). Kari D. Roberts et al. compared the effect of fentanyl and atropine to a combination of fentanyl and atropine with Mivacurium on changes in arterial oxygen saturation, finding that the use of atropine and fentanyl without muscle relaxant is associated with successful intubation and diminished fluctuations in arterial oxygen saturation (22). In Friesen and Thieme's study, 20% of neonates intubated with atropine had hypertension (23). Other studies have also reported that the use of atropine can reduce bradycardia in response to vagal stimulation and help regulate heart rate during hypoxia (24-25). However, the results of the present study are not aligned with those reported in these studies. Here, no statistically significant difference was observed between mean blood pressure and heart rate in the use of fentanyl or remifentanil and a combination of remifentanil and atropine during the intubation. However, as Figure 3 shows, in patients receiving fentanyl premedication, there was no increase in heart rate immediately after the intubation, probably due to the lower tension applied to the patient during the intubation.

This randomized controlled trial was conducted on 20 preterm infants to compare the use of morphine and midazolam versus remifentanil and midazolam for intubation. No difference was observed between groups in terms of pain control or hemodynamic parameters, but the possibility of seamless intubation conditions was significantly higher with remifentanil than with morphine. All infants treated with remifentanil and midazolam were intubated at the first attempt while only 60% of the infants treated with morphine and midazolam did so. (26)

A cohort study of 33 preterm and term infants intubated after receiving a combination of atropine, fentanyl, and a paralytic agent showed that fentanyl induced no significant adverse effects. Remifentanil, another synthetic opiate with a rapid onset of action and a short duration of action, has been shown to be an effective drug for neonatal intubation. (27).

According to data, Remifentanil and fentanyl alleviated BV2 microglial morphological injury induced by Lipopolysaccharides and suppressed inflammatory releases. Considering the comparable effects of both drugs, the clinical results do not seem to be promising (28-29)

One strength of the present study is that it overcame the limitations of previous studies by simultaneously comparing the effects of fentanyl and remifentanil, two common opioid analgesics available in the NICU wards, and looked into the effect of atropine in combination with remifentanil as a premedication in two hospitals and a university-affiliated training center.

An important limitation of this study was irregular monitoring and the measurement of blood levels after administering these drugs. By determining blood levels, more profound insights can be gained about the function of each drug.

Conclusion

Based on the results of this study, it seems that remifentanil plus atropine is an effective drug for premedication in non-emergency intratracheal intubation of neonates with slight changes in blood oxygen saturation and a better level of arterial blood oxygen saturation up to 30 min after the extubation. Also, comparing the effects of fentanyl, and remifentanil plus atropine on other hemodynamic variables in neonates did not exhibit a significant difference.

Acknowledgments

The authors wish to thank the Clinical Research Development Unit of Children Hospital, University of Medical Sciences, Tabriz, Iran, for its scientific support.

Conflicts of interest

The authors declare they have no conflict of interest, financial or otherwise.

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