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Original article

Remifentanil versus Fentanyl for pain control during elective endotracheal intubation for surfactant administration in preterm infants

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Abstract

Introduction: Today, the reality of pain in neonates is an undisputed fact, but pain management in clinical practice remains a challenging issue. All neonatal units should have a pain management protocol. The aim of this study was to compare the effectiveness of Remifentanil versus Fentanyl in pain control during elective endotracheal intubation for surfactant administration in preterm infants.

Materials and methods: Preterm infants with gestational age between 28 weeks and 34 weeks + 6 days with Respiratory Distress Syndrome (RDS) who needed surfactant administration were divided into two groups using a random sampling method. Neonates in the first group received 2 μg/kg intravenous Fentanyl infusion and neonates in group 2 received 1 μg/kg intravenous Remifentanil before elective endotracheal intubation for surfactant therapy. The vital signs, including heart rate, oxygen saturation, mean arterial blood pressure and change in facial grimace were documented in an unnamed Premature Infant Pain Profile-Revised (PIPP-R) scoring sheet individually. Video recording was performed in both groups before, during and after the endotracheal intubation. All videos and data were interpreted and scored by two Newborn Individualized Developmental Care and Assessment Program (NIDCAP) professionals.

Results: The mean PIPP-R score in the Fentanyl-treated group was 13.06 ± 3.55 and in the Remifentanil-treated group was 10.75 ± 2.93, with no statistically significant difference (p = 0.054). There was less need for Naloxone use in the Remifentanil group (p < 0.001). Incidence of apnea, severe drop in oxygen saturation, Intra-Ventricular Hemorrhage (IVH) and chest rigidity were not significantly different between the two groups.

Conclusion: Although the difference was not statistically significant, Remifentanil reduced the pain score more than Fentanyl during elective endotracheal intubation in preterm infants. We recommend conducting further studies with larger study populations to determine the better drug and the optimal dosage of these drugs in neonates.

Keywords

Preterm infants, endotracheal intubation, Fentanyl, Remifentanil, Premature Infant Pain Profile – Revised, surfactant.

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Introduction

Our knowledge of pain and its management has increased significantly over the past two decades [1]. Today, the reality of pain in neonates is undisputed, but pain management in clinical practice remains as a challenging issue [2].

Preterm infants receive several painful procedures during hospitalization in Neonatal Intensive Care Units (NICU). Exposure to repeated painful stimuli can lead to serious consequences. There is growing concern about the long-term effects of repeated pain in newborns, which include emotional, behavioral and learning problems [3-5]. The American Academy of Pediatrics (AAP) and the Canadian Pediatric Society (CPS) have also suggested that all neonatal units should have a pain management protocol [3].

A large number of preterm infants are intubated for respiratory care such as surfactant therapy or mechanical ventilation. The most important complications of intubation without pain control include laryngospasm, reflective bradycardia, respiratory depression, hypotension, gastrointestinal and neurologic complications [6]. Opioids are effective medications for the control of moderate to severe pain in neonates. They produce both analgesia and sedation and their therapeutic window is wide. They decrease the physiologic stress responses [3]. Fentanyl and its shorter-acting derivatives (Remifentanil) are often used for analgesia prior to procedures in preterm and term newborns. Remifentanil has unique pharmacokinetic characteristics such as rapid and uniform clearance by unspecific esterases and a highly predictable onset and offset of effect. It has a rapid onset of action (60-90 seconds) and at adequate doses it renders the patient motionless, thus eliminating the need for a muscle relaxant. There is conflicting evidence on the efficacy and adverse effects of different opioids as premedication drugs in preterm infants. A randomized control trial found that overall intubating conditions (easy laryngoscopy, opened vocal cords and a completely relaxed jaw) were improved significantly in those receiving Remifentanil vs. Morphine [7]. Remifentanil was reported as an effective opioid in neonates and is more potent than Fentanyl [3, 8, 9]. On the other hand, as one of the steps in implementation of developmental care in the Tabriz Alzahra Teaching Hospital, we needed to find a more effective and safe method of pain control during elective intubation. The aim of this study was to compare the effectiveness of Remifentanil versus Fentanyl for pain control during elective endotracheal intubation for surfactant administration in preterm infants.

Materials and methods

Study populations

This Randomized Clinical Trial was conducted from September 2016 to October 2017 in the Alzahra Teaching Hospital located in Tabriz, Iran. Inclusion criteria were: preterm infants with gestational age between 28 weeks and 34 weeks + 6 days who were

inborn, whose respiration was supported by nasal Continous Positive Airway Pressure (nCPAP) because of Respiratory Distress Syndrome (RDS) and who needed surfactant administration with the INSURE method (INtubation, SURfactant, Extubation). The diagnosis of RDS was based on a history of early onset respiratory distress with compatible radiologic findings and the diagnosis was confirmed by an experienced neonatologist. RDS was managed in accordance with the *European Consensus Guidelines on the Management of Respiratory Distress Syndrome – 2016 Update* [10].

Exclusion criteria were: other causes of respiratory distress in newborns, second or third-degree AV heart block, previous use of analgesics, APGAR score under 5 at 5 minutes after delivery, impaired consciousness level, major congenital anomalies, difficult intubation due to orofacial anomalies and more than three attempts at intubation. In this study, we assessed 98 infants requiring intubation with diagnosis of RDS. Forty-two infants were selected for the study and, after obtaining written consent, they were randomized in two groups, treated respectively with Fentanyl and Remifentanil (**Fig. 1**).

Study design

The random selection of the patients was based on computer-generated random numbers. The neonates in group 1 received 2 μg/kg intravenous Fentanyl (Fenijject®, manufactured by the Aburaihan Pharmaceutical company, Tehran, Iran),

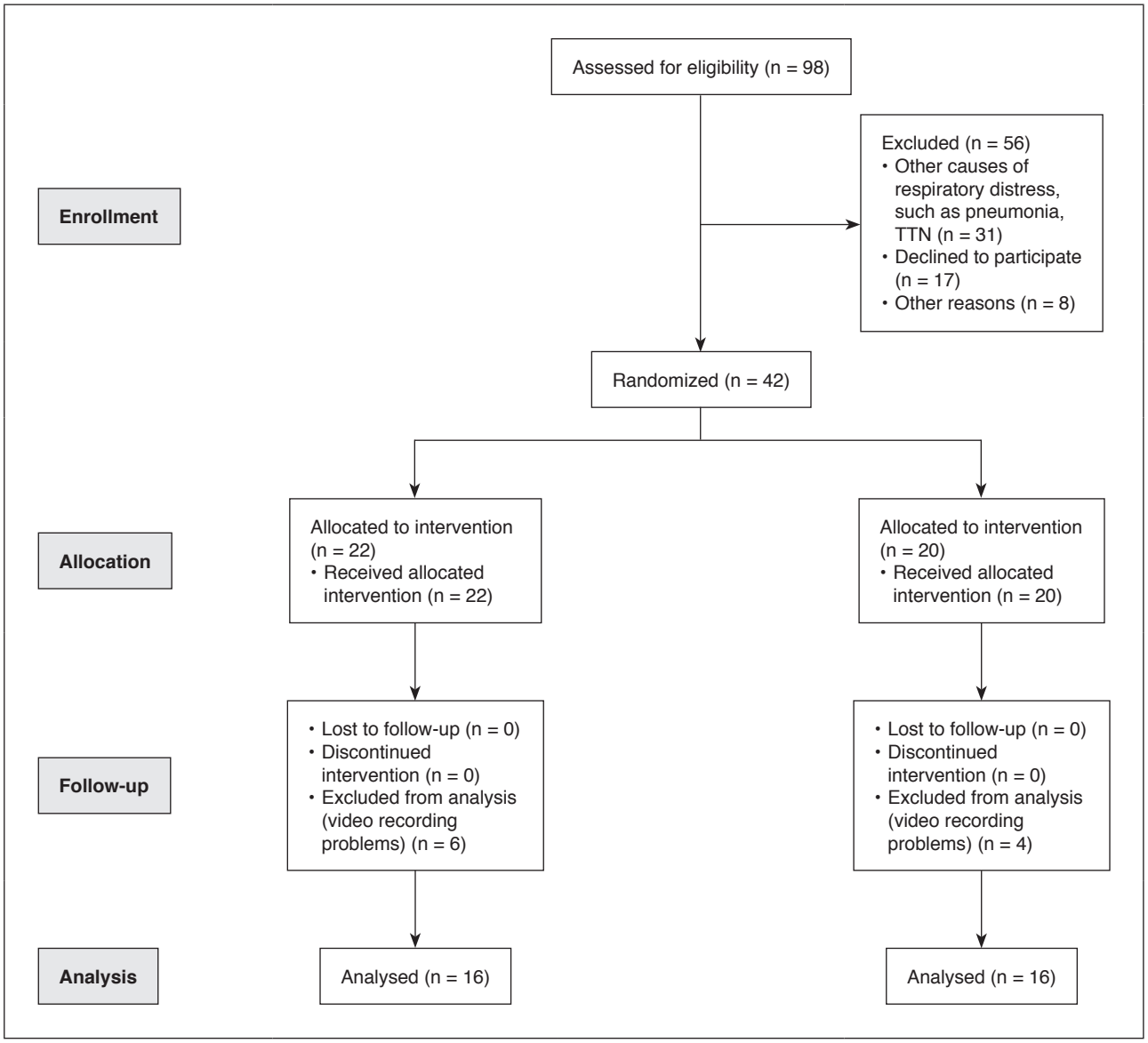

Figure 1. Consort diagram of the study.

while those in group 2 received 1 μg/kg intravenous Remifentanil (Ultiva®, manufactured by Mylan® Pharmaceuticals Inc., West Virginia, USA). The dose of 1 μg/kg of Remifentanil was chosen after a pilot study that had found that 2 μg/kg of the drug was accompanied by apnea and significant decrease in oxygen saturation in most of the infants. Therefore, we selected the lowest recommended dose of Remifentanil. Infusion time in both groups was around 2 minutes [11]. To ensure the onset of the drug's effect in the Fentanyl and Remifentanil group, we waited 5 and 2 minutes, respectively, after completion of the drug infusion. All intubations were performed by the same neonatology fellow. All events were recorded before, during and after the intubation by a camera. The vital signs monitored were heart rate, oxygen saturation and Mean Arterial Pressure (MAP). Their changes were documented in a not-named Premature Infant Pain Profile – Revised (PIPP-R) scoring sheet for each infant prior, during and after drug administration. The duration of intubation was recorded by a stopwatch from the moment the blade of the laryngoscope was inserted into the infant's mouth until its removal. If the intubation procedure lasted more than 30 seconds, it was discontinued and a second attempt was made [6]. We used Poractant Alfa (Curosurf®) surfactant in this study. After surfactant injection via tracheal tube and verification of spontaneous respirations, the infants were extubated. In the absence of spontaneous respiration, Naloxone (Naloxan T.D.®, Tolidaru, Saveh, Iran) was injected at a dose of 0.1 mg/kg within 1 minute by intravenous infusion and the infant was reassessed for effective spontaneous respirations [6, 12]. All videos and data were interpreted and scored by two Newborn Individualized Developmental Care and Assessment Program (NIDCAP) professionals, who were unaware of the type of drugs used in infants. Data collected includes: MAP, heart rate, the amount of oxygen saturation before, during and after intubation, the number of attempts at intubation and the length of time taken for successful intubation for each infant. In this study, the severity of pain was scored based on the PIPP-R, which consists of 7 items including gestational age, baseline behavioral state, change in heart rate, decrease in oxygen saturation, brow bulge, eye squeeze and nasolabial furrow [13]. The pain score was considered the primary outcome in this study. A trained radiologist performed brain ultrasonography for evaluation of IntraVentricular Hemorrhage (IVH) between 3 and 5 days after birth.

The sample size was determined based on the results of the pilot study, involving five infants for each group. The mean score of PIPP-R in the first group (treated with Fentanyl) was 10.44 ± 1.81; in the second group (treated with Remifentanil) it was 12.00 ± 1.58. Considering $\alpha = 0.05$ and power of 80% and 2 units difference, 14 samples for each group (28 total samples) were estimated. In order to increase the validity of the study, 16 samples were selected for each group (32 total samples). This study was registered in the Iranian Randomized Clinical Trial (IRCT) with number IRCT201310164113N7. The Regional Ethics Committee of Tabriz Medical University approved the trial by IR code IR.TBZMED.REC.1395.993.

Statistical analysis

The statistical analysis was performed using SPSS® software version 16. Data were analyzed via N (%) and mean ± SD. The differences between the two groups were identified using ANOVA. The chi-square or Fisher's exact tests were used for comparison of categorical variables. The differences were considered to be significant at $p \leq 0.05$.

Results

Both groups of patients had similar demographic characteristics at baseline (**Tab. 1**). The

Table 1. Baseline demographic characteristics of the infants in the Fentanyl-treated and Remifentanil-treated groups.

Characteristic	Fentanyl-treated group (n = 16)	Remifentanil-treated group (n = 16)	p-value
Gestational age (weeks)	31.50 ± 2.75	31.94 ± 2.14	0.62
Gender (male/female)	8/8	8/8	
Baseline heart rate (beat/minute)	142.18 ± 17.74	147.12 ± 14.04	0.43
Baseline SpO_2 (%) under nCPAP	94.81 ± 4.05	94.56 ± 3.18	0.84
Baseline mean blood pressure (mmHg)	49.50 ± 10.80	50.88 ± 17.69	0.58

nCPAP: nasal Continous Positive Airway Pressure.

mean gestational age was 31.5 ± 2.75 weeks in the Fentanyl-treated group and 31.94 ± 2.14 weeks in the Remifentanil-treated group (p = 0.62). The mean PIPP-R score was 13.06 ± 3.55 in the Fentanyl group and 10.75 ± 2.93 in the Remifentanil group, with no statistically significant difference (p = 0.054) (**Fig. 2**). The mean number of attempts for successful endotracheal intubation was 1.06 ± 0.25 in the Fentanyl group and in 1.25 ± 0.44 in the Remifentanil group (p = 0.15). The mean time necessary for successful intubation was 32.50 ± 15.54 seconds in the Fentanyl group and 30.25 ± 16.90 seconds in the Remifentanil group (p = 0.40).

There was no apnea after surfactant injection in the Fentanyl-treated group, but in the Remifentanil-treated group 3 cases of apnea were reported (p = 0.22). The heart rate (beat/min) before intubation in the Fentanyl-treated group and Remifentanil-treated group was 142.18 ± 17.74 and 147.12 ± 14.04, respectively (p = 0.43). Maximum heart rate during intubation in the Fentanyl-treated group and the Remifentanil-treated group was 143.67 ± 15.45 and 149.25 ± 16.79, respectively (p = 0.34). Minimum heart rate during intubation in the Fentanyl-treated group and the Remifentanil-treated group was 136.80 ± 14.45 and 134.81 ± 28.06, respectively (p = 0.80). The oxygen saturations (%) before and during intubation in the Fentanyl-treated group were 94.81 ± 4.05 (%) and 87.13 ± 6.90 (%), respectively (p < 0.001), and in the group treated with Remifentanil were 94.56 ± 3.18 (%) and 80.38 ± 12.09 (%), respectively (p < 0.001). However, the difference between the oxygen saturation change before and after intubation in the two groups was not statistically significant (p = 0.25) (**Fig. 3**). There was no chest rigidity in any infant. There were no statistically significant differences in frequency of IVH between the two groups (p = 0.50). All of the Fentanyl-treated patients (100%) and 6 of the patients (37.5%) in the Remifentanil group required Naloxone use (p < 0.001).

The mean blood pressures before and after endotracheal intubation in the Fentanyl-treated group were 49.50 ± 10.80 mmHg and 55.69 ± 19.52 mmHg, respectively (p = 0.21). The mean blood pressures before and after tracheal intubation in the group treated with Remifentanil were 50.88 ± 17.69 mmHg and 51.50 ± 11.97 mmHg, respectively (p = 0.86). The difference between blood pressure change before and after intubation in the two groups was not statistically significant

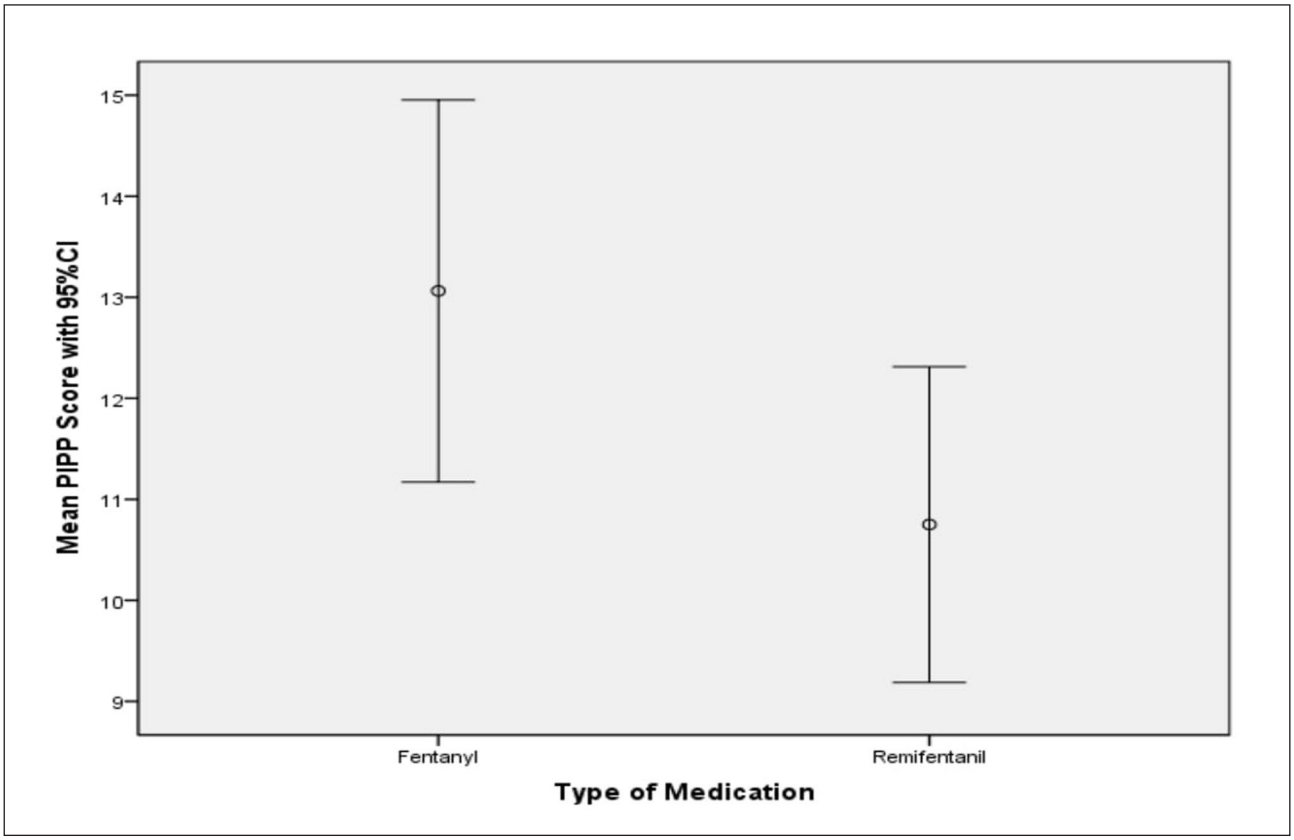

Figure 2. Error bar of PIPP-R scores in the Fentanyl-treated and Remifentanil-treated groups.

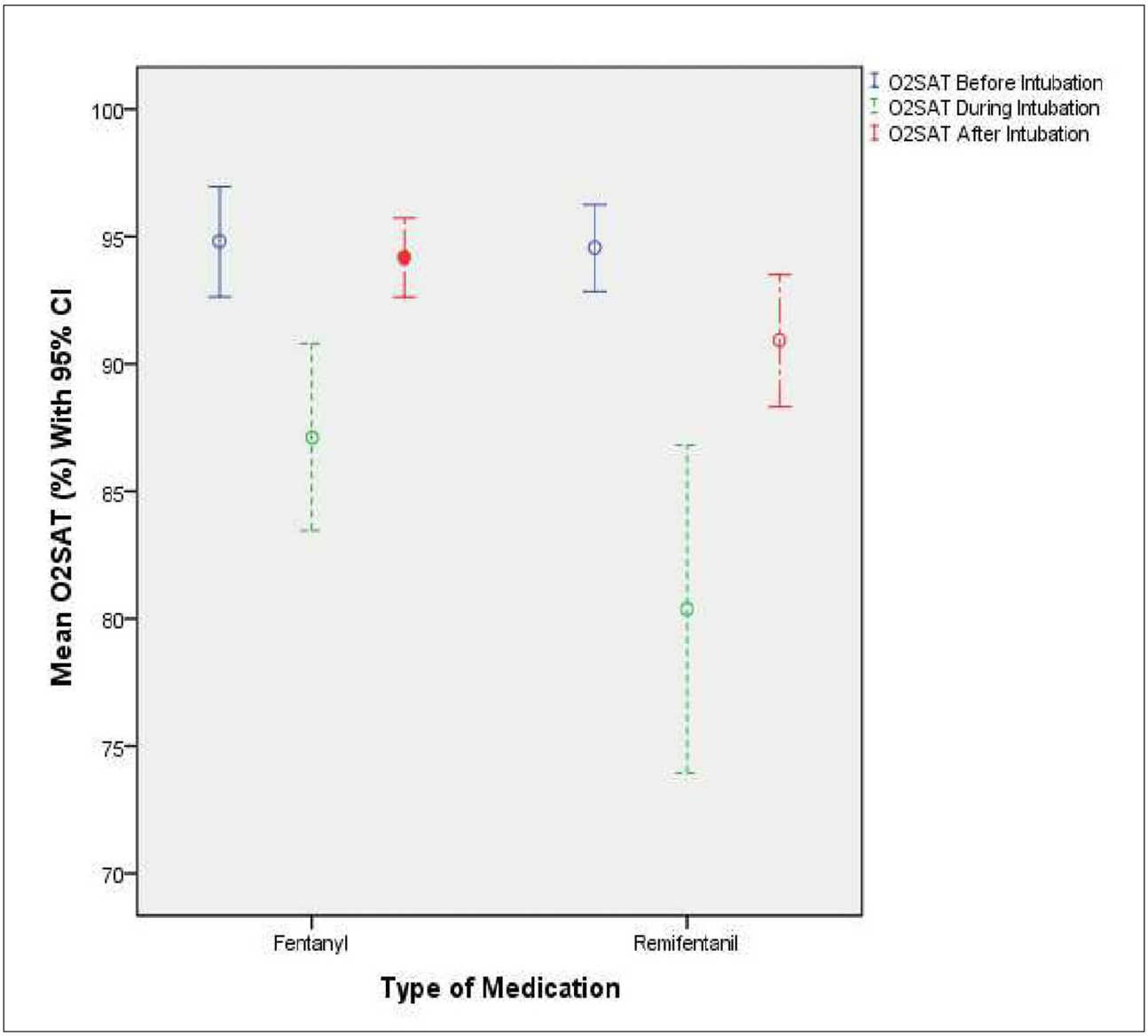

Figure 3. Error bar of oxygen saturation changes before, during and after intubation in the Fentanyl-treated and Remifentanil-treated groups.

(p = 0.63) (**Fig. 4**). Study results are summarized in **Tab. 2**.

Discussion

In our study, Remifentanil reduced the pain score more than Fentanyl during elective endotracheal intubation, albeit not to a statistically significant degree. The rates of complications in both groups were similar. Fentanyl is a synthetic opioid and has a significant effect on the μ-receptor. Fentanyl's margin of safety is wide and it has beneficial effects on hemodynamic stability. Fentanyl has a short duration of action and a rapid onset. Chest wall rigidity is an adverse effect of Fentanyl with high bolus dosing (> 5 μg/kg), but it may occur even with low doses (1-2 μg/kg) with a rapid infusion [2]. Fentanyl's onset and duration of action are 1-5 minutes and 15-30 minutes, respectively [6].

Remifentanil is a new high potency opioid that is a selective μ-receptor agonist. Its metabolism is independent of renal and hepatic function. Remifentanil reacts with nonspecific esterase in tissue and erythrocytes. Intravenous doses of 0.25 μg/kg/min would seem to be effective and safe in neonates, but data on the use of Remifentanil in neonates are scarce [2]. Remifentanil's onset and duration of action are 0-2 minutes and 3-5 minutes, respectively [6].

Thus, Remifentanil use would seem to have some advantages over Fentanyl. 1) Unlike Fentanyl, the metabolism of Remifentanil is not hepatic, and it is

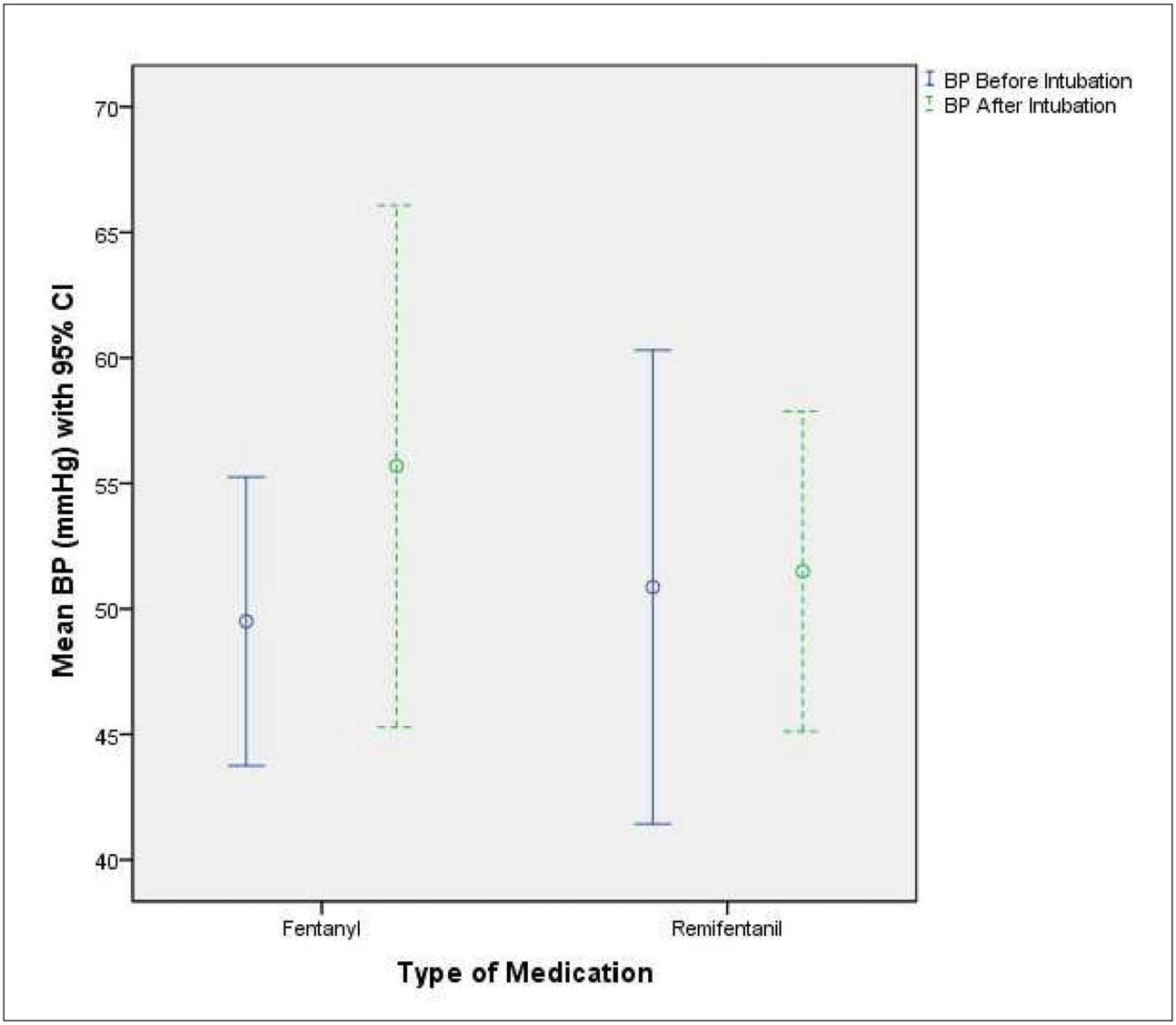

Figure 4. Error bar of blood pressure changes before and after intubation in the Fentanyl-treated and Remifentanil-treated groups.

Table 2. Study results in two Fentanyl-treated and Remifentanil-treated groups.

Outcome	Fentanyl-treated group (n = 16)	Remifentanil-treated group (n = 16)	p-value
PIPP-R score	13.06 ± 3.55	10.75 ± 2.93	0.054
Attempts for successful endotracheal intubation	1.06 ± 0.25	1.25 ± 0.44	0.15
Time spent for successful intubation (seconds)	32.50 ± 15.54	30.25 ± 16.90	0.40
Incidence of apnea after surfactant administration	0 (0%)	3 (18.75%)	0.22
Maximum heart rate during intubation (beat/minute)	143.67 ± 15.45	149.25 ± 16.79	0.34
Minimum heart rate during intubation (beat/minute)	136.80 ± 14.45	134.81 ± 28.06	0.80
SpO_2 (%) during intubation	87.13 ± 6.90	80.38 ± 12.09	0.65
Mean blood pressure after intubation (mmHg)	55.69 ± 19.52	51.50 ± 11.97	0.61
Chest rigidity	0 (0%)	0 (0%)	
IVH	2 (12.5%)	3 (18.75%)	0.50
Need for Naloxone use	16 (100%)	6 (37.5%)	< 0.001

PIPP-R: Premature Infant Pain Profile-Revised; IVH: IntraVentricular Hemorrhage.

metabolized by unsaturated esterases of blood and tissues, which are sufficiently present in the infant. 2) Renal clearance of all analgesic drugs other than Remifentanil decreases in the neonatal period [6, 8]. 3) In the Remifentanil group, due to the shorter duration of action compared with Fentanyl, there is less need for the use of Naloxone. Naloxone may cause severe complications such as cardiac arrest, pulmonary edema and seizures [14, 15].

In a study by Badiee et al. in 2013, 40 preterm neonates requiring endotracheal intubation were studied in two groups. One group received 10 μg/kg of atropine and 2 μg/kg Remifentanil infusion in 2 minutes and the control group received 10 μg/kg of atropine and 2 ml of normal saline. The study used the Premature Infant Pain Profile (PIPP) scoring scale. It showed that the babies receiving Remifentanil had significantly less pain compared to the control group without significant alterations in mean blood pressure and oxygen saturation [6]. That study compared Remifentanil vs. placebo (normal saline). In our study, we compared Remifentanil vs. Fentanyl and we used PIPP-R for pain scoring. We did not use atropine as a premedication drug.

In another study performed by Choong and colleagues in 2009, in one group 15 neonates were treated with Remifentanil (3 μg/kg) and normal saline. The other group was treated with Fentanyl (2 μg/kg) and succinylcholine (2 mg/kg). The main aim of that study was assessment of successful intubation time; the secondary goals were assessment of the time of spontaneous breathing, and of changes in heart rate, level of oxygen saturation and blood pressure during the procedure. The median time for successful intubation in the two groups was not significantly different (247 seconds in the Remifentanil-treated group and 156 seconds in the Fentanyl-treated group). Chest wall rigidity was more common in the Remifentanil-treated group, although the difference was not statistically significant. They concluded that, although physiological changes were similar in both groups, chest rigidity at doses of 3 μg/kg Remifentanil was worrisome and more studies were needed to evaluate the ideal dosage of the drug [8]. It should be noted that, in their study, successful intubation was considered as the primary outcome and the evaluation of the pain score was not the goal of the study. Moreover, in their study, endotracheal intubations were performed by different operators with different skills. In this study, we considered the pain score as the primary outcome and all the intubations were performed by the same experienced operator.

It is noteworthy that the dose of Remifentanil for infants was 1-3 μg/kg in most references [11]. In our pilot study, we used an average dose of 2 μg/kg of Remifentanil. It was accompanied with a significant decrease in oxygen saturation during intubation and in apnea after use of the drug. In 2007, Pereira e Silva and colleagues found lower doses of Remifentanil to be effective and associated with fewer side effects in neonates [7]. On the other hand, we know Remifentanil's potency is twice that of Fentanyl [3] and like other opioids, Remifentanil can also cause drug-dependent apnea, respiratory depression, hypotension and bradycardia. Skeletal muscle rigidity may be caused by intravenous administration of more than 1 μg/kg or by an infusion rate above 0.1 μg/kg/min [9]. This is why in this study the dose of 1 μg/kg was selected for the infants in the Remifentanil group. Although not statistically significant, 3 cases of apnea were reported with the slow infusion of 1 μg/kg Remifentanil in our study.

Conclusions

Although not statistically significant, Remifentanil reduces the pain score more than Fentanyl during elective endotracheal intubation in preterm infants. We recommend conducting further studies with larger study populations for determining the better drug and the optimal dosage of these drugs in neonates.

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Declaration of interest

The Authors declare that there is no conflict of interest.

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