The effect of low dose fentanyl as a premedication before induction of general anesthesia on the neonatal apgar score in cesarean section delivery: randomized, double-blind controlled trial

Seyyed Hasan Karbasy¹, Pooya Derakhshan*²

Abstract
Background: The administration of opioids before induction of general anesthesia can be considered as a problem in cesarean section. The aim of this study was to compare the effects of intravenous Fentanyl as a premedication before induction of general anesthesia versus placebo on maternal hemodynamic parameters and on the first and fifth minutes Apgar score in the neonates in elective cesarean delivery.

Methods: This double-blinded, randomized, clinical trial study was conducted in 2014-2015 at Vali-e-Asr hospital, Birjand, Iran. Ninety full term pregnant women undergoing elective cesarean section delivery under general anesthesia were selected. The participants were randomly classified into two groups: The Fentanyl group and the placebo. Intravenous Fentanyl 1μg/kg was administrated three minutes before anesthesia induction for the Fentanyl group, and 2 milliliter normal saline was administered for the placebo group. Maternal mean arterial pressure, heart rate before the start of anesthesia induction and thirty seconds after intubation were measured. Also, the first and fifth minutes Apgar scores of the neonates were evaluated and recorded by a blinded anesthesiologist. The clinical trial registration number was IRCT2015010320112N3.

Results: Maternal mean arterial pressure was significantly lower in the Fentanyl group than the placebo group after intubation. Heart rate was significantly higher in the placebo group before the start of anesthesia induction and after intubation compared to the Fentanyl group. The first and fifth minutes’ Apgar scores of the neonates were not statistically different between the two groups.

Conclusion: Administration of 1μg/Kg intravenous Fentanyl before the induction of anesthesia for cesarean section delivery decreases maternal hemodynamic changes after intubation. In addition, it does not have any effect on Apgar scores of the neonate in the 1st and 5th minutes after birth.

Keywords: Fentanyl, Apgar score, Cesarean section, Anesthesia, Neonates.

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Introduction
There is still debate on the methods to induce analgesia during cesarean section delivery by general anesthesia (1-3). The best anesthesia technique is provided when analgesia, hypnosis, amnesia and muscle relaxation are gathered together for the patients. Opioids are the gold standard to achieve analgesia during general anesthesia (4). However, in the cesarean section delivery, there is a concern about depressant effects of opioids on fetus and neonates’ central nerves system. Synthetic opioids like Fentanyl has high lipid solubility and can easily pass through the maternal-placental blood barrier and result in central nerves system and respiratory depression in the neonates. Therefore, anesthesiologists do not use opioids for the mothers before delivery (5). On the other words, stress response to intubation and surgical stimulation can cause epinephrine and norepinephrine release and decreases the utroplacental blood flow and fetus’s oxygenation by vas-
oconstriction (1). Furthermore, pain after surgery has many adverse effects like decreased mobility of the patient, affecting the maternal care of the newborn. Severe postoperative pain can be a source of complications like longer postoperative hospital stay and increased nosocomial infections, hypoxemia, atelectasis, decreased diaphragmatic movement and increased incidence of nausea and vomiting. Administration of opioids can cause primitive analgesia and reduce the mentioned complications (6-8).

Fentanyl is a synthetic lipid-soluble opioid that can produce 30-60 minutes of analgesia in adults. Fentanyl does not have any active metabolite with a half time of 70-440 minutes in the newborn (5). Use of Fentanyl for painless vaginal delivery has been studied without much maternal and neonatal adverse effects (9).

The first and the fifth minutes Apgar scores after delivery are commonly used to determine the need for resuscitation and newborn’s short and delayed neurologic outcomes. A restricted amount of studies support the use of opioids in the induction of general anesthesia for cesarean section (10).

The aim of this study was to examine the effects of administering intravenous Fentanyl as a premedication before induction of general anesthesia on maternal hemodynamics and first and fifth minutes Apgar scores of the newborns compared to placebo in elective cesarean section delivery.

### Methods

#### Data

This double-blind, randomized, clinical trial was conducted in 2014-2015, at Vali-e-Asr hospital, Birjand, Iran. All patients signed the informed consent. The Ethics Committee of Birjand University of Medical Sciences approved the principle of the study protocol. The clinical trial registration number was IRCT2015010320112 N3. The inclusion criteria were full term pregnant woman aged 18–45, classified as American Association of Anesthesiologist (ASA) I and II who were candidates for elective cesarean section delivery under general anesthesia. The exclusion criteria were fetal distress, opium or sedative drugs abuse, emergency situation, uterus incision to fetus delivery time> 3 minutes, fetal anomalies or any congenital syndromes, rupture of membranes up to 3 hours, history of complicated general anesthesia (difficult intubation, acetylcholine stares deficiency and any history in association with malignant hyperthermia), twin pregnancy, preeclampsia or eclampsia, cardiovascular disease, allergy to any of the study medications and respiratory disease. A total of 113 patients aged 18-45 who were candidates for an elective cesarean section surgery and categorized as American Society of Anesthesiologist Class I and II were admitted to the hospital. Of them, 17 were excluded according to the exclusion criteria; from the remaining 96, 90 patients were randomly selected (Fig. 1). Using a computer generated random number, the selected patients...
were randomly categorized into two groups of control (n:45) and Fentanyl (n:45). The same surgeon and anesthesiologist performed the surgery for all the patients. In all the patients, an intravenous line was accessed by a 20-gauge catheter, and the infusion of NaCl 0.9% 5Ml/Kg was started. All patients were monitored by pulse oximetry, electrocardiogram lead II, noninvasive blood pressure and capnography (Saadat, Alborz II). Heart rate and mean arterial pressure were measured and noted before administration of any drug. Isoflurane 0.8% and N2O-O2 50% were used for anesthesia maintenance. in the Fentanyl group, after five minutes of pre-oxygenation, the patients were given 1 microgram per kilogram Fentanyl (50microgram/milliliter, Darou Darman Pars Co., Tehran, Iran), and in the placebo group, 2milliliter of normal saline were injected intravenously. After two minutes, anesthesia was induced by thiopental Na 4 (Mg/Kg) (injection powder 1 gr, Sandoz, Austria) and succinylcholine 1.5 (Mg/Kg) (suxamethonium chloride, Biologici, Italy). Tracheal intubation was done after 30 seconds and was checked by end tidal CO2 monitoring. Based on the study of Maghsoudloo et al.(5) with an α=0.05 and a β=0.1 and 90% power and δ=1 and σ=1.1 Apgar score, the sample size was calculated from the below formula: N=2 (zα + zβ)² / (δ/σ)² (11). Thus, n1 and n2 were calculated as 43, giving us a total sample size of 86. To achieve more precision, the final sample size was decided to be 90 (45 in each case and control groups). Before start of the operation and 30 seconds after intubation, hemodynamic parameters (HR, MAP) were measured and noted by another blinded anesthesiologist. The patients were blind because of the same syringe, color and volume of fentanyl and normal saline administered.

Atracurium 0.2mg/Kg/IV, Fentanyl 1μg/Kg/IV, midazolam 2Mg/IV and oxytocin 50 units in 500milliliter ringer IV were administered after the fetus delivery and umbilical cord clamping.

The first and the fifth minutes Apgar scores of the neonates were evaluated and noted. All data were measured and noted by another blinded anesthesiologist. The study variables were age, weight, homodynamic status (mean arterial pressure and heart rate before induction of anesthesia, after intubation and five minutes after start of operation), and the first and five minutes Apgar score were.

**Statistical Analysis**

Data were analyzed using SPSS18 software. Differences were tested by independent-sample t-test, Fisher and Chi-Square tests and were considered statistically significant at p<0.05.

**Results**

The baseline characteristics of the study participants were not statistically different (Table 1). The Apgar scores at the first (p=0.5) and the fifth minutes (p=0.8) were similar among the groups, and all the neonates had scores ≥8 at 5th min (Table 2).

The mean maternal arterial pressure was significantly lower in the Fentanyl group than the placebo group after intubation (108±21 versus 120±20 p=0.006). Similarly, the difference in the mean arterial pressure was significant between the two groups (-1.2±2.3 in the Fentanyl group versus 0.4±1.4 in the placebo group p<0.001). The heart rates of the participants before the start of anesthesia and after intubation were significantly higher in the placebo than the Fentanyl group (9.8±6.3 versus -0.22±22

### Table 1. Patients characteristics and neonate apgar score

| Variable            | Fentanyl group | Placebo group | p    |
|---------------------|----------------|---------------|------|
| Age (Y)             | 28.6±5.0       | 30.1±5.9      | 0.2  |
| Wight (Kg)          | 73.2±16.5      | 75.6±10.5     | 0.4  |
| Height (Cm)         | 156.7±2.1      | 156.6±2.8     | 0.7  |
| Gestational age (W) | 39.1±0.9       | 38.8±0.7      | 0.5  |

Y: Year, Kg: Kilogram, Cm: Centimeter, W: Week
No significant difference was detected between the two groups in HR before induction of anesthesia and after intubation and after five minutes from start of the operation (p>0.05). In addition, no statistically significant differences were found between the two groups in the maternal mean arterial blood pressure before induction of anesthesia and after five minutes from the start of the operation (p>0.05) (Table 3).

**Discussion**

Decreasing stress response is the goal in all surgeries because of many short-term and long-term complications due to this reaction (7,10). In cesarean delivery under general anesthesia, the way to reduce these stress responses is still unclear (3). Numerous studies have displayed that preemptive analgesia results in diminishing afferent pain signals in the direction of spinal cord, which seems to be more effective than controlling the pain after its initiation (12-16). However, the risk of depressant effect of opioids on the neonate limits its use Nevertheless, the release of epinephrine and norepinephrine in response to intubation and skin incision may reduce the placental blood flow and decrease fetus oxygenation. To prevent the mentioned reactions, many drugs like Ketamine, Alfentanile, Mepridine, NSAIDs and Teramadol are used (2,17).

In this study, we found that administration of low dose of Fentanyl does not have any significant effect on Apgar score in the first and fifth minutes. However, hemodynamic variables (HR and MAP) were significantly lower in the Fentanyl group.

Likewise, in a study by Sabri et al. it was shown that use of Nalbuphine before the induction of general anesthesia reduces homodynamic response to intubation and surgery. However, neonatal Apagar score was lower in the Nalbuphine group compared to the placebo group in contrast to our results (1).

Moreover, in a study conducted by Maghsoudloo et al., administration of 1μg/Kg intravenous Fentanyl, three minutes before induction of anesthesia for cesarean section resulted in better maternal hemodynamic control with no significant effect of low dose Fentanyl on Apagar score (5).

Several studies have shown that use of Fentanyl to reduce the pain of delivery in mothers may not affect the Apagar score in the newborns, and it is not necessary to use Naloxone for central system depression (18). Marwah R et al., found that intravenous patient-controlled analgesia with both Remifentanil or Fentanyl offers a moderate degree of labor analgesia, but brief maternal oxygen desaturation is observed more frequently with Remifentanil. Fentanyl is associated with a more need for neonatal resuscitation (19).

**Conclusion**

We demonstrated that use of low dose Fentanyl is safe in cesarean section delivery and does not have any effect on the neonatal apgar score.
Apgar score in the first and fifth minutes. In addition, the use of Fentanyl has advantages on maternal stress response to intubation. Further studies are needed to find the best method to achieve pain relief and reduce the stress response during the first minutes of cesarean section delivery without any effect on Apgar score of the neonates.

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