

Does Intravenous Fentanyl Affect Apgar Scores and Umbilical Vessel Blood Gas Parameters in Cesarean Section Under General Anesthesia?

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Abstract- The administration of opioids during induction of general anesthesia is a matter of challenge in obstetric anesthesia. The aim of this study was to investigate the effects of intravenous fentanyl before induction of general anesthesia on the "1st and 5th minutes' Apgar scores" in neonates with elective cesarean surgery. In a double blinded randomized clinical trial on 60 parturients undergoing elective cesarean surgeries under general anesthesia in Vali-e-Asr Hospital, in Tehran, Iran, were divided randomly into two groups; the intervention group and the control. In intervention group, intravenous fentanyl 1µg/kg was administered three minutes before anesthesia induction. The induction route, laryngoscopy and tracheal intubation were the same in the groups. The blood pressure (BP) and heart rate (HR) measures were recorded before anesthesia induction (as baseline measures) and so during laryngoscopy and intubation. The 1st and 5th minute's apgar scores and the pH of umbilical cord arterial and venous samples were compared in two groups. The systolic and diastolic blood pressure, mean arterial pressure and heart rate changes before and after induction and in various times after intubation showed significant difference between two groups ($P < 0.05$). The 1st and 5th minute's Apgar scores of the neonate and umbilical cord arterial and venous blood gas analysis were not statistically different between two groups ($P > 0.05$). Based on the results of this study, the administration of 1 µg/Kg intravenous Fentanyl, three minutes before induction of anesthesia for cesarean section can lead to a stable hemodynamic situation in mother and showed no effects on neonate's outcomes. Fentanyl showed no effects on Apgar scores and on umbilical cord arterial and venous blood gases analysis and it probably can be used safely in elective cesarean surgeries. More studies are required to obtain a clear view.

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Introduction

Induction of general anesthesia (GA) in cesarean surgeries and the use of opioid drugs during obstetric anesthesia is one of challengeable issues among anesthesiologists (1). The anesthesia technique should prevent maternal awareness while providing adequate oxygenation for her fetus and avoiding depressant effects when passing through the placenta (2). Although the cesarean possesses a considerable percentage of surgeries, because of umbrage about adverse effects of opioids on fetus and neonates, these drugs are not used routinely before induction of anesthesia. However there is umbrage about use of premedication before induction of anesthesia in pregnant women who are candidate for

cesarean surgery. Opioids, because of lipid solubility, can easily pass through the maternal- placental barrier and can lead to adverse effects such as decreasing in Apgar score and respiratory depression in new born neonates. Fentanyl is a synthetic opioid which was produced by Janson in 1950 in Belgium. This drug has an analgesic potency 50-100 times more than morphine (3). Intravenous (IV) administration of Fentanyl can create a short onset analgesia effect lasting about 30-60 minutes. No active metabolites are produced with the metabolism of Fentanyl (4). In neonates, Fentanyl has a half time of 70-440 minutes, which results in low side effects. Devoid of long effects on neonates is of specificities of Fentanyl which makes it a suitable opioid for usage in labor when general anesthesia is

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required (5). Neonate's outcome is usually assessed by Apgar score and the blood gas analysis of umbilical cord vessels is a method for assessment of fetal distress. Measurement of blood gas items in hazardous labors and in depressed neonates is an important issue (6). Apgar score assessment in the first and the fifth minutes after delivery are the commonest method for clinical assessment and neurologic outcome determination after labor (7). A limited number of studies have been already performed which support unwary use of opioid in obstetric anesthesia induction. (8).

The opioid usage might potentially be associated with decreasing the amount of required drugs for maintenance of anesthesia, making stable hemodynamic conditions during laryngoscopy and intubation, and declining in maternal stress. This study is proposed to investigate the effects of administering intravenous Fentanyl before induction of general anesthesia on first and fifth minutes' Apgar scores in comparison to placebo in elective cesarean surgery based on the importance of Apgar score, and the analysis of umbilical cord arterial and venous samples in newborn evaluation.

Materials and Methods

In this double blinded randomized clinical trial, between 2008 and 2009, 60 patients who were candidate for elective cesarean surgery in vali-e-Asr Hospital, Tehran, Iran, were enrolled in study using a sequential sampling. All ASA class I-II mothers that candidated for cesarean section under general anesthesia, while the fetus was not in distress based on biophysical profiles, enrolled in study. Those without an informed consent, maternal ages >35 years, ASA class \geq III, fetal distress (based on NST, CST and FHR), emergent situations (e.g. maternal bleeding), opium or sedative drugs abuse, fetus exit time > 8 min, fetal anomaly or congenital syndromes, long term rupture of membranes, history of complicated general anesthesia, and the preeclampsia-eclampsia cases excluded from the study.

The study protocol was approved by ethics committee of Tehran University of Medical Sciences and each parents signed informed consent before enrollment in the study. The selected patients were randomly categorized into two groups, the control (I) and the intervention (II), using block randomization in blocks containing four patients and non-blinded. For all the patients, the operation and anesthesia were performed by the same surgeon and anesthetist. After pre-oxygenation for 5 minutes, and access to iv line and under essential monitoring including automated non-

invasive blood pressure monitoring (NIBP), the baseline hemodynamic parameters such as HR, systolic and diastolic blood pressure, and mean arterial pressure recorded using automated non-invasive blood pressure monitoring (ANIBP), in five stages: 1) after pre-oxygenation and just before fentanyl/ or placebo injection, 2) just before induction, 3) just before laryngoscopy & intubation, 4) One minute after endotracheal intubation 5) Five minutes after endotracheal intubation. Anesthesia induction performed in all patients in same method, Rapid Sequence anesthesia (RSA), using Thiopental sodium (Thiopentone, Sandoz GmbH, Koundl, Austra) 5 mg/kg and after loss of consciousness, Succinylcholin (Suxamethonium Chloride, Succinyl, Sidefarma, S.A, Portugal) 1mg/Kg/IV administrated under cricoids pressure to facilitate tracheal intubation. Anesthesia maintained with 0.5 MAC Isoflurane and N₂O/O₂ combination (each one 50%). Cis-Atracurium 0.6 mg/Kg/IV and Fentanyl 2 μ g/Kg/IV administered after fetus delivery and umbilical cord clamping.

The First and the fifth minutes' Apgar scores, blood gas of umbilical arterial/ and venous samples of neonates were assessed and analyzed in the groups. Samples from umbilical vein and artery were collected immediately after clamping of the cord. These samples were sent to assess the blood gas parameters.

The Apgar score at minute one assessed by a gynecology resident and the fifth minute's Apgar score assessed by an anesthesia resident. These residents were not aware of the patients' group. All data was recorded in prepared checklists and were coded for statistical analysis.

Results were reported as mean \pm standard deviation (SD) for quantitative variables and percentages for categorical variables. The groups were compared using the Student's t-test and repeated measurement ANOVA for continuous variables and the Chi-square test (or Fisher's exact test if required) for categorical variables. All the statistical analysis were performed using SPSS version 13 (SPSS Inc, Chicago, IL, USA) for Windows. *P* values of 0.05 or less were considered statistically significant.

Results

Figure 1 to 5 shows systolic and diastolic blood pressure, Mean Arterial Pressure, heart rate, and spo₂ changes in five time intervals in the groups, all of them were significantly less than control group in intervention mothers.

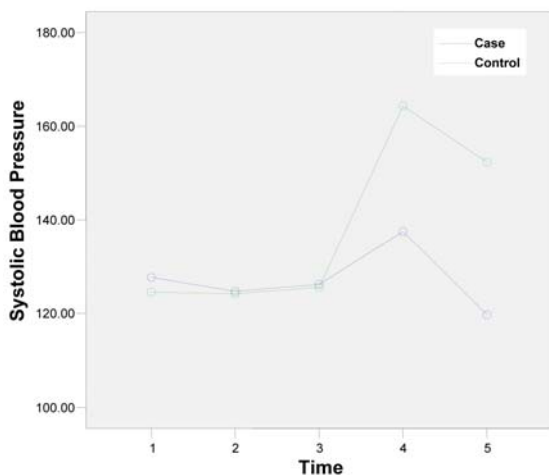


Figure 1. Systolic blood pressure changes before and after anesthesia induction in various time intervals in two groups ($P=0.001$)

Time intervals: 1) after pre-oxygenation and just before Fentanyl/ or placebo injection. 2) Just before induction. 3) Just before laryngoscopy & intubation.

4) One minute after endotracheal intubation. 5) Five minutes after endotracheal intubation.

Table 1. The demographic data of the study patients

Variable	Case(n=30)	Control (n=30)	P value*
Age	28 ± 5	27.9 ± 4.8	0.938
Weight (Kg)	72.4 ± 6.0	73.5 ± 6.7	0.518
Height (cm)	162.8 ± 4.8	162.8 ± 4.3	0.977
Parity	1.4 ± 0.5	1.3 ± 0.5	0.434

* Student's t-test, $P<0.05$ assumed meaningful

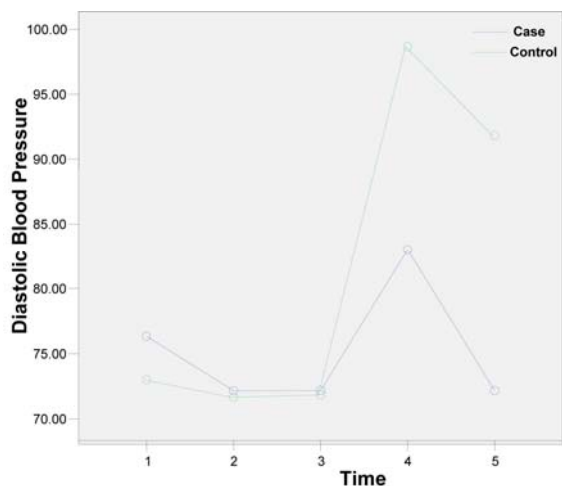


Figure 2. Diastolic blood pressure changes before and after anesthesia induction in various time intervals in two groups ($P=0.001$)

Time intervals: 1) after pre-oxygenation and just before Fentanyl/ or placebo injection. 2) Just before induction. 3) Just before laryngoscopy & intubation.

4) One minute after endotracheal intubation. 5) Five minutes after endotracheal intubation.

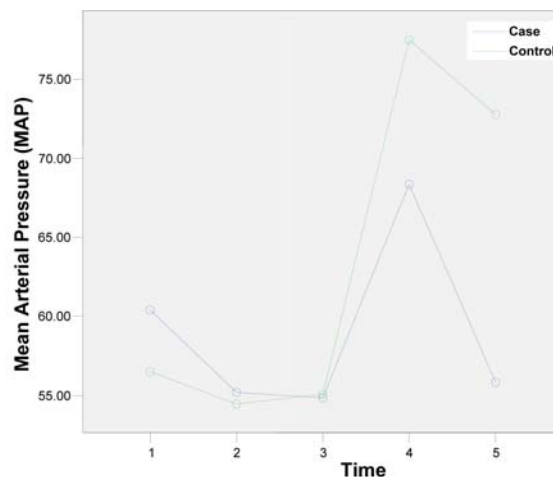


Figure 3. MAP changes before and after anesthesia induction in various time intervals in two groups ($P=0.001$)

Time intervals: 1) after pre-oxygenation and just before Fentanyl/ or placebo injection. 2) Just before induction. 3) Just before laryngoscopy & intubation.

4) One minute after endotracheal intubation. 5) Five minutes after endotracheal intubation.

There were no significant differences in spo2 changes among two groups in above five time intervals. The Demographic characteristics of mothers, first and fifth minutes' Apgar scores, Arterial and venous blood gases analysis of umbilical cord vessels are summarized in tables 1 to 4, the differences were not statistically significant ($P>0.05$).

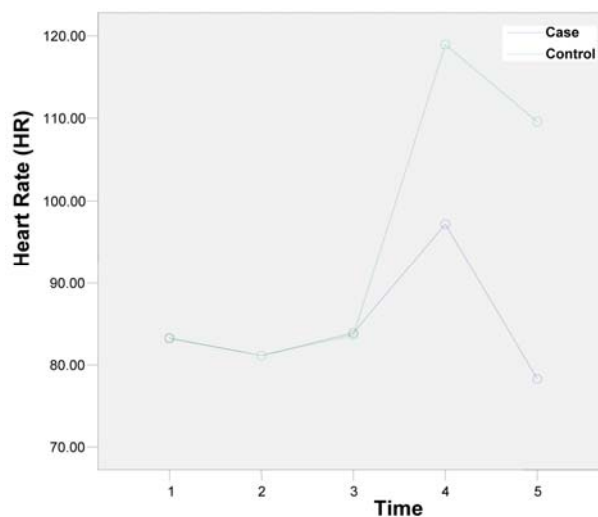


Figure 4. Heart rate changes before and after anesthesia induction in various time intervals in two groups ($P=0.001$)

Time intervals: 1) after pre-oxygenation and just before Fentanyl/ or placebo injection. 2) Just before induction. 3) Just before laryngoscopy & intubation.

4) One minute after endotracheal intubation. 5) Five minutes after endotracheal intubation.

Effect of intravenous fentanyl on apgar scores

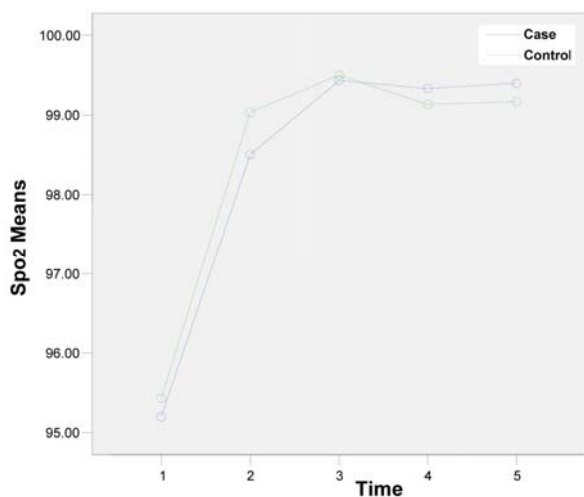


Figure 5. SpO₂ changes before and after anesthesia induction in various time intervals in two groups ($P=0.654$)

Time intervals: 1) after pre-oxygenation and just before Fentanyl/ or placebo injection. 2) Just before induction. 3) Just before laryngoscopy & intubation.

4) One minute after endotracheal intubation. 5) Five minutes after endotracheal intubation.

Table 2. Comparison of the first and fifth minutes Apgar scores in two groups. (Mean ± SD)

Group	Case	Control	P Value*
Apgar			
First minute's	8.7 ± 0.5	8.5 ± 0.5	0.197
Fifth minute's	9.7 ± 0.5	9.8 ± 0.4	0.229

*Student's t-test. $P < 0.05$ assumed meaningful

Table 3. Comparison of umbilical cord arterial blood gas (ABG) analysis in two groups. (Mean ± SD)

Group	Case	Control	P Value*
ABG Analysis			
pH	7.3 ± 0.02	7.3 ± 0.03	0.361
PCO ₂	50.4 ± 6.3	48.3 ± 5.4	0.171
Base excess	-2.8 ± 1.6	-3 ± 1.2	0.447
HCO ₃	24 ± 3	23 ± 3	0.140
PaO ₂	22.7 ± 4	23.3 ± 4.8	0.618
SaO ₂	32.6 ± 9.1	36 ± 12	0.199

*Student's t-test. $P < 0.05$ assumed meaningful

Discussion

In this study, systolic blood pressure changes before and after induction of anesthesia and in one and five minutes after intubation in intervention group was significantly less than control group. Diastolic BP, MAP and heart rate changes in group I were also considerably lesser than group II before and after induction and so one and five minutes after intubation.

Table 4. Comparison of umbilical cord Vein blood gases analysis in two groups (Mean ± SD)

Group	Case	Control	P Value*
ABG Analysis			
pH	7.3 ± 0.02	7.3 ± 0.02	-
PCO ₂	43.8 ± 4.7	42.7 ± 5.2	0.402
Base excess	-4.3 ± 7.7	-3.2 ± 1.7	0.455
HCO ₃	23.3 ± 1.9	23.2 ± 2.3	0.927
PaO ₂	33.9 ± 5.4	33.2 ± 5.5	0.646
SaO ₂	57.8 ± 10	57.02 ± 10.7	0.766

*Student's t-test. $P < 0.05$ assumed meaningful

Case: 1 Mic/kg iv-Fentanyl before anesthesia induction for elective cesarean section.

Control: Equal volume of iv-Normal saline before anesthesia induction or elective cesarean section.

These changes for SpO₂ were not statistically different in two groups. Various studies have been reported that Fentanyl can lead to stable hemodynamics in cesarean surgeries (9). Because of sympathomimetic effects of tracheal intubation, a considerable rise in BP and HR occurs after intubation, Fentanyl results in decreasing the responses to intubation. Fentanyl through the mechanism of baroreflex depression can lead to decline in cardiac output. It seems that Fentanyl decreases the hypertensive response of laryngoscopy and tracheal intubation (10).

Some studies confirmed that Fentanyl in comparison with Meperidine is associated with lower side effects and has shorter acting time in obstetrics and delivery (11). Fentanyl with the dose of 50-240 µg/hr is not associated with complications for mother and neonate in term labors (11). IV administration of Fentanyl is clinically effective in gynecology (11) and its safety has been proved in neonates (12).

One study revealed that intravenous Fentanyl in doses of 50, 75 and 100 µg have not significant effects on acid-base and cardiovascular parameters of mother and fetus (4). In our study, the first and the fifth minutes Apgar scores in new borne did not show a significant difference between two groups. This is in consistent with other studies (4). Some studies reported that Apgar score in neonates whose mothers received Fentanyl during labor did not differ significantly with those did not (4). There are a variety of studies which revealed neonatal Apgar scores more than 7 and no need for Narcan use in neonates whose mothers had received intravenous Fentanyl (13-15). Garner E *et al.* demonstrated that these neonates despite of no need for Narcan, had first- and fifth-minutes Apgar scores of 5 and 7 respectively (16).

First-minute Apgar score was less than 7 in 11% of neonates in Garner E *et al.* study and one neonate had fifth minute Apgar score less than 7 which was not related to Fentanyl (17). It seems that Fentanyl is not associated with long time effects on neonates; its short acting time and rapid metabolism result in less depression among neonates (18,19).

Blood gases analysis in neonates after elective cesarean surgery without labor showed higher pH, PaO₂, base excess and HCO₃ and lower PCO₂ in comparison to normal adults (20,21). In our study blood gas Analysis of umbilical cord artery did not revealed a significant difference in pH, PCO₂, base excess, HCO₃, PaO₂ and SpO₂ between two groups. These parameters were not statistically differing in analysis of venous blood gases of umbilical cord too. It seems that due to the rapid metabolism of Fentanyl, since its injection to entrance to the fetus body- a few amounts of this drug reaches to the fetus which do not affect fetus health.

Arterial PH is the most advantageous parameters of umbilical arterial blood and is associated with neonate's neurological development (22,23). However some studies do not confirm it (24,25). There is not an international consensus about lower pH threshold for the definition of acidosis during labor (pH 7-7.20) (26). The pH per se can show the degree of acidosis but cannot define the cause. Respiratory acidosis is more hazardous for fetus and neonates than the metabolic one (26). Respiratory acidosis is due to CO₂ concentration which is usually secondary to umbilical cord compression, low cardiac output and inadequate placental perfusion (26). The pH and arterial gas analysis of umbilical cord are impressed during labor process (27).

Based on the results of our study the administration of 1 µg/kg Fentanyl intravenously, three minutes before induction of anesthesia, leads to a stable hemodynamic situation in mothers, probably due to sympathetic suppression and showed no adverse effects on neonate's apgar scores. Both arterial and venous blood gas analysis of umbilical cord are important to get information about the neonate's situation. Fentanyl with above dose showed no adverse effects on the new born Apgar scores at first and fifth minutes after birth and showed no significant effect on umbilical cord's arterial and venous blood gases parameters while provided a smooth hemodynamic condition for mothers during and after laryngoscopy and tracheal intubation in elective cesarean section. The exact effects and the recommendation to routine use of this drug in elective cesarean surgeries needs to be evaluated.

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Effect of intravenous fentanyl on apgar scores

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