Clinical Investigation

The effect of alfentanil on maternal haemodynamic changes due to tracheal intubation in elective caesarean sections under general anaesthesia

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ABSTRACT

Background and Aims: Endotracheal intubation can produce severe maternal haemodynamic changes during caesarean sections under general anaesthesia. However, administration of narcotics before endotracheal intubation to prevent these changes may affect the Apgar score in neonates. This study was designed to evaluate the effect of intravenous alfentanil on haemodynamic changes due to endotracheal intubation in elective caesarean sections performed under general anaesthesia. **Methods:** Fifty parturients were randomly divided into two equal groups. Patients in the first group received alfentanil 10 μg/kg and in the second group received placebo intravenously 1 min before induction of anaesthesia for elective caesarean section. Haemodynamic parameters and bispectral index system (BIS) in mothers, peripheral capillary oxygen saturation (SpO_2) and Apgar score in the newborn were assessed. **Results:** Changes in systolic blood pressure were significant at 1, 5 and 10 min after intubation between two groups. Changes in diastolic blood pressure were significantly less in alfentanil group, 1 min after induction of anaesthesia and 1 min after endotracheal intubation. Mean heart rate at 1 min after induction and at 1 and 5 min after intubation also reduced significantly in this group. **Conclusion:** Alfentanil use was associated with decreases or minimal increases in maternal systolic and diastolic blood pressures and heart rate after endotracheal intubation.

Key words: Alfentanil, apgar score, blood pressure, caesarean section, endotracheal intubation, general anaesthesia, heart rate, laryngoscopy, pregnancy

INTRODUCTION

Although the use of general anaesthesia for caesarean delivery has dramatically declined during recent decades, it is still necessary for the management in conditions such as maternal haemorrhage, overt coagulopathy, life-threatening foetal compromise, maternal heart diseases, patient refusal for regional anaesthesia, etc.[1,2] Regional anaesthesia may be an alternative to general anaesthesia in selected patients with dilated or restrictive cardiomyopathy. However, the need for anticoagulant therapy may limit this option.[2] During pregnancy, several haemodynamic changes including increased intravascular volume and heart rate exacerbate the cardiovascular aberrations associated with heart disease.[3] Opioids administered before caesarean section under general anaesthesia reduce maternal stress response related to intubation and surgery but may decrease the Apgar score after delivery and when opioids are used, all measures for neonatal monitoring and neonatal resuscitation must be available.[4]

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Direct laryngoscopy and passage of a tracheal tube are noxious stimuli that can provoke adverse cardiovascular and other system changes. These haemodynamic changes can result in myocardial ischemia but seem to cause little harm to most patients.[1] However, they are undesirable in patients with cardiac disease. It is possible to separate the factors that contribute to the haemodynamic response. Haemodynamic changes start within seconds of direct laryngoscopy, and there is a further increase in heart rate and blood pressure with passage of the tracheal tube.[1]

Many techniques have been tried in an effort to attenuate adverse haemodynamic responses to intubation, but none is ideal in pregnancy. Prevention of these responses by increasing depth of anaesthesia with the use of inhalational agents is attractive in theory. However, changes in the concentration of volatile anaesthetic agents in blood and at effector sites occur slowly in relation to the onset and offset of airway stimuli and haemodynamic responses. In this regard, use of N_2O with a volatile agent may be beneficial.[1]

With regard to the ever present risk of respiratory depression in parturients and decrease Apgar score in the neonates because of opioids, agents of short onset and offset of effects such as remifentanil or alfentanil seems to be of great advantage.[1]

Thus, we decided to study the effect of low dose of short-acting opioid alfentanil on haemodynamic changes due to tracheal intubation during general anaesthesia for caesarean sections.

METHODS

This study was performed after obtaining the permission of the institution's human subjects committee and the informed consent of the participants. In this randomised, double-blinded, controlled clinical study, 50 pregnant patients (gravida 1 or 2) between the ages of 18 and 40 years, scheduled for elective caesarean section, were assigned to two equal groups (using colour cards).

This study was powered on the basis of previous results showing 12% decrease in heart rate after endotracheal intubation in parturients who received opioids as premedication. With $\alpha = 0.05$ and $\beta = 0.2$, sample size was calculated to be 25 patients in each group.[5]

Those patients with a positive history of cardiovascular disease, consumers of antihypertensive, sedative, analgesic, antihistaminic and psychoactive drugs were excluded from this study. Difficult intubation, more than one attempt of laryngoscopy, long-duration laryngoscopy (more than 15 s), uterine incision-delivery time more than 90 s and induction-delivery time more than 5 min were other exclusion criteria.

One minute before induction of anaesthesia, patients in the first group received intravenous alfentanil 10 μg/kg, diluted in normal saline (total volume of 10 ml) for premedication and patients in the second group received 10 ml normal saline as placebo.

For induction of anaesthesia, all patients received sodium thiopentone 5 mg/kg and succinylcholine 1.5 mg/kg. During maintenance of anaesthesia, atracurium 0.5 mg/kg, isoflurane 1 minimum alveolar concentration and O_2–N_2O (50–50%) were used. Haemodynamic parameters in this study were measured at different time periods from the time of injection of premedication until 50 min after endotracheal intubation.

Bispectral index system (BIS®) (Aspect Medical Systems, Inc., A-2000™ BIS XP Model) was used to assess depth of anaesthesia and awareness. Oxygen saturation (SpO_2) and Apgar score were determined in neonates.

After neonatal delivery, patients in two groups received the same dose of oxytocin, midazolam and fentanyl. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) for windows version 16.0 software, Chicago, SPSS Inc.

Analysis of variance, *t*-test, Fisher's exact test and Chi-square test were used for analysis of the data. $P < 0.05$ was considered statistically significant.

RESULTS

The study spanned from March 2013 to March 2014. Mean of age (years) of patients was 28.4 ± 5.77 in alfentanil group and 27.12 ± 5.79 in placebo group. Average weight (kg) of patients was 75.8 ± 10.4 in alfentanil group and 80.4 ± 7.5 in placebo group. The two groups were comparable with respect to pre-operative haemodynamic parameters and BIS® [Table 1].

The mean systolic blood pressure changed minimally in alfentanil group as compared to placebo group at 1 min ($P = 0.0001$), 5 min ($P = 0.000$) and 10 min ($P = 0.01$) after endotracheal intubation [Figure 1].

The mean diastolic blood pressure showed significant statistical differences between the two groups only 1 min after induction of anaesthesia ($P = 0.04$) and 1 min after endotracheal intubation ($P = 0.00$) [Figure 2]. There were significant statistical differences between the two groups in regard to mean heart rate 1 min after induction of anaesthesia ($P = 0.01$), 1 min after endotracheal intubation ($P = 0.000$) and 5 min after endotracheal intubation ($P = 0.04$) [Figure 3]. Mean BIS® values were not significantly different between the two groups ($P = 0.3$) [Figure 4].

Mean of neonatal Apgar scores at 1 and 5 min and neonatal SpO_2 were not significantly differerent between the two groups [Table 2]. One patient in placebo group had awareness during anaesthesia, but none patients in alfentanil group developed awareness.

DISCUSSION

Physiochemical properties in pharmacokinetics are a function of molecular structure. Fentanyl and its derivatives are tertiary amines. Alfentanil is the only derivative of this series for which the un-ionised form predominates at the physiologic pH. Thus, alfentanil is more diffusible than fentanyl and sufentanil, and it reaches its peak of effect rapidly.[1]

Because alfentanil penetrates the brain so rapidly, equilibration of alfentanil between plasma and the

Table 1: Comparison of pre-operative haemodynamic parameters and BIS®

Variable	Group alfentanil (*n*=25)	Group placebo (*n*=25)	*P*
Systolic blood pressure (mmHg)	126±9.75	118±7.57	0.09
Diastolic blood pressure (mmHg)	79.6±10.10	77±10.29	0.37
Heart rate (beat/min)	98.32±11.63	92±13.37	0.08
BIS®	97±1.47	98.24±1.66	0.06

Values are expressed in mean±SD. SD – Standard deviation; BIS® – Bispectral index system

Table 2: Comparison of neonatal Apgar score and SpO_2

Variable	Group alfentanil (*n*=25)	Group placebo (*n*=25)	*P*
Apgar score at 1 min	8.92±0.27	8.88±0.33	0.646
Apgar score at 5 min	10±0.00	9.88±0.33	0.544
SpO_2	89.79±3.37	88.72±5.56	0.418

Values are expressed in mean±SD. SD – Standard deviation

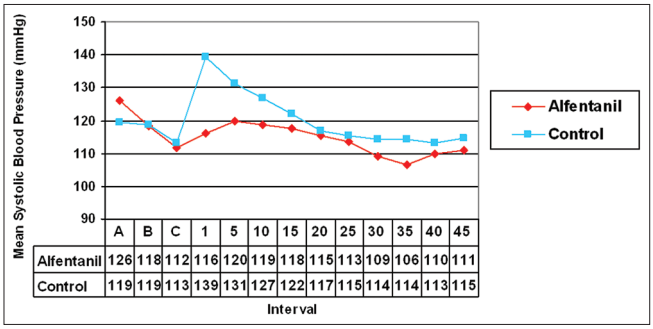

Figure 1: Comparison of mean of systolic blood pressure in two groups (A) 1 min before drug administration, (B) 1 min after drug administration, (C) 1 min after induction of anaesthesia, 1–45 Min after endotracheal intubation

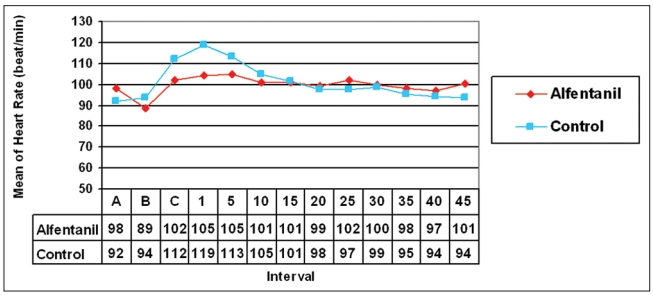

Figure 3: Comparison of mean of heart rate in two groups (A) 1 min before drug administration, (B) 1 min after drug administration, (C) 1 min after induction of anaesthesia, 1–45 Min after endotracheal intubation

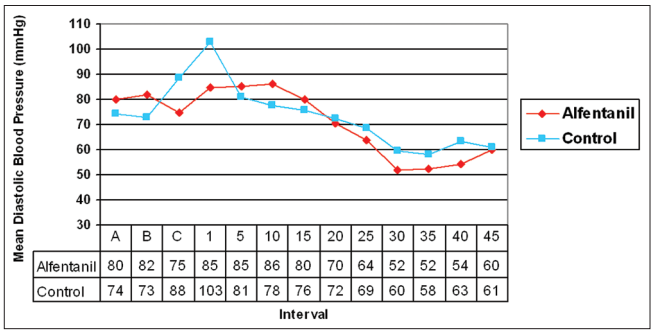

Figure 2: Comparison of mean of diastolic blood pressure in two groups (A) 1 min before drug administration, (B) 1 min after drug administration, (C) 1 min after induction of anaesthesia, 1–45 Min after endotracheal intubation

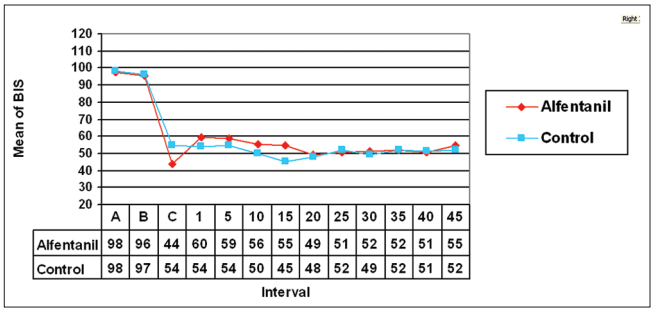

Figure 4: Comparison of mean of bispectral index system in two groups (A) 1 min before drug administration, (B) 1 min after drug administration, (C) 1 min after induction of anaesthesia, 1–45 Min after endotracheal intubation

central nervous system can be achieved while plasma alfentanil levels are quite high relative to those of sufentanil and fentanyl. This property explains the efficacy of alfentanil, administered just before or simultaneously with a sedative-hypnotic.[1]

In our study, the effect of intravenous alfentanil on haemodynamic changes due to endotracheal intubation during elective caesarean section was evaluated.

There were no significant statistical differences among the two groups regarding age, weight, BIS and maternal pre-operative haemodynamic parameters.

Following alfentanil administration, systolic blood pressure decreased at 1, 5 and 10 min after endotracheal intubation. Diastolic blood pressure decreased only 1 min after intubation and heart rate decreased 1 and 5 min after intubation. So, we can say that alfentanil (10 μ/kg) prevented exaggerated haemodynamic responses to endotracheal intubation in our patients. With respect to maternal BIS®, neonatal Apgar score and SpO_2, similar changes were seen in the both groups.

The study did not include emergency surgeries which was the main limitation of our study, where poor control of haemodynamics preoperatively would be a problem. In order to increase the accuracy and reduce bias of this double-blind study, we instructed only one researcher to record the haemodynamic parameters and BIS in parturient and also Apgar score and SpO_2 in neonates.

Potential problems associated with general anaesthesia for caesarean section include failed intubation, pulmonary aspiration of gastric contents, neonatal depression, maternal awareness and haemodynamic instability especially during laryngoscopy and tracheal intubation.[1] In general anaesthesia for caesarean section, it should be better to use techniques and medications which maintain stable maternal haemodynamic function, provide adequate depth of anaesthesia, prevent maternal awareness, provide adequate oxygenation for the foetus and avoid foetal depression.

In general, we use opioids as premedication for general anaesthesia. The opioid usage might be associated with reduced maternal anxiety, making stable haemodynamic conditions during laryngoscopy and endotracheal intubation and decreasing anaesthetic requirement for maintenance of anaesthesia. Administration of opioids before induction of general anaesthesia is a matter of challenge in obstetric anaesthesia.

Opioids, because of their lipid solubility, can easily pass through the maternal-placental barrier and decrease Apgar score by producing respiratory depression in neonates. However, the endotracheal intubation-induced catecholamine secretion can result in foetal arrhythmia.[6,7] Thus, the sympathetic-suppressing role of opioids seems to be crucial in pregnant patients. There are many other approaches to reduce haemodynamic responses during endotracheal intubation. Aerosol or other application of topical anaesthetics may be beneficial with a low risk of adverse effects.[1]

Combinations of topical anaesthetics with other drugs may be useful. Drugs such as labetalol and esmolol that act on the cardiovascular system can reduce either the blood pressure or heart rate responses and have been recommended particularly in combination with narcotics.[1] Narcotics with short onset and offset of effects such as remifentanil seem to be of great advantage and suitable for usage in labour when general anaesthesia is required.[8-10]

Alfentanil is bound to plasma proteins (mostly glycoprotein) in higher proportions (90%) than fentanyl. At physiologic pH, it is mostly (90%) un-ionised because of its relatively low pK_a (6.5). Thus, despite more intense protein binding, alfentanil's diffusible fraction is higher than that of fentanyl. This explains, in part, its short latency to peak effect after intravenous injection. The main metabolic pathways of alfentanil are similar to those of sufentanil and include oxidative N-dealkylation and O-demethylation, aromatic hydroxylation and ether glucuronide formation. The degradation products of alfentanil have little, if any, opioid activity.[1]

Safavi *et al*. showed that some drugs such as nitroglycerin are effective in attenuating the pressor response to tracheal intubation in severe pre-eclampsia and could be used instead of opioids to control haemodynamic responses.[11] Maghsoudloo *et al*. demonstrated that administration of 1 μg/kg fentanyl intravenously 3 min before induction of anaesthesia leads to stable haemodynamic situation in mothers.[12]

Hosseini *et al*. studied the effect of remifentanil on haemodynamic parameters of parturients and Apgar score of the neonate in elective caesarean section under general anaesthesia. They concluded that remifentanil (0.7 μg/kg) controls haemodynamic change in parturients without producing adverse effects on Apgar scores of neonates.[13]

Pournajafian *et al*. compared the effect of remifetanil versus fentanyl regarding haemodynamic changes due to endotracheal intubation in pre-eclamptic parturients for caesarean delivery. They found that remifentanil (0.05 μg/kg/min for 3 min before induction and continued until intubation time) can be used in parturients for delivery under general anaesthesia to prevent severe increase in blood pressure and heart rate during tracheal intubation without adverse effects on newborn.[8] Remifentanil has unique pharmacokinetics properties. Its effects are altered negligibly by liver or kidney disorders and age variations, and is associated with rapid recovery.[9,10]

CONCLUSION

Use of alfentanil (10 μg/kg) as premedication decreased maternal systolic, diastolic blood pressure and heart rate in the 1st min of general anaesthesia for caesarean sections. This result is important because the most critical time of maternal haemodynamic changes during caesarean section under general anaesthesia is during and immediately following tracheal intubation.[1] The Apgar score and SpO_2 in the newborn and maternal BIS® were not affected.

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Conflicts of interest

There are no conflicts of interest.

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