Clinical Investigation

Efficacy and safety of low-dose ketamine as an adjunct analgesic and amnesic during caesarean section under general anaesthesia

Address for correspondence:
Dr. Sunil Rajan,
Department of Anaesthesiology and Critical Care,
Amrita Institute of Medical Sciences, Kochi, Kerala, India.
E-mail: sunilrajan@aims.amrita.edu

Sunil Rajan, Anwar Hassain, Nitu Puthenveettil, Lakshmi Kumar
Department of Anaesthesiology and Critical Care, Amrita Institute of Medical Sciences, Kochi, Kerala, India

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ABSTRACT

Background and Aims: The practice of avoiding sedatives or anxiolytics during caesarean section under general anaesthesia (GA) until delivery of the baby could result in exaggerated haemodynamic responses and an increased risk of awareness. We aimed to assess the efficacy and safety of low-dose ketamine, used as an adjunct analgesic and amnesic, in attenuating these responses during caesarean section under GA. **Methods:** This prospective, randomised study was conducted in 40 patients. Group K ($n = 20$) received 0.25 mg/kg ketamine, whereas Group C received 5 ml normal saline intravenously (IV) just before induction of anaesthesia. After intubation, patients were ventilated with O_2 and N_2O (40:60%) with 0.7% end-tidal isoflurane. Fentanyl and midazolam were given following delivery of the baby. Mann–Whitney and Fisher's exact tests were used for statistical analysis. **Results:** Preinduction haemodynamic parameters and those recorded at 1 min after induction were comparable in both groups. However, heart rate and systolic blood pressure recorded after intubation (at 3, 5, 7, 9, 12, 15, 20, 30 and 45 min after induction) showed significantly high values in Group C ($P < 0.05$). Mean arterial pressure also showed a similar pattern. Umbilical vein pO_2, pCO_2 and pH were comparable in both groups. Though Apgar score at 1 min showed a higher scoring in Group K, at 5 min both groups had comparable scores. In Group C, intraoperative lacrimation (50% vs. 0%) and hallucinations/recall of intraoperative events (10% vs. 0%) were high. **Conclusion:** IV ketamine 0.25 mg/kg can be safely used as an adjunct analgesic and amnesic to attenuate haemodynamic responses during caesarean section under GA without affecting the foetal outcome.

Key words: Awareness, caesarean section, general anaesthesia, ketamine

INTRODUCTION

The risks of exaggerated haemodynamic responses during anaesthesia and surgery and development of awareness has been a cause for concern in patients undergoing caesarean section, concurrent to the practice of avoidance of sedatives and anxiolytics until delivery. Laryngoscopy and intubation causes exaggerated haemodynamic responses and monitoring indices, such as the bispectral index (BIS)[1] and auditory evoked potential index,[2] have shown these patients to be in lighter planes of anaesthesia. Potential benefit can be obtained by the addition of an agent that could enhance analgesia and amnesia without adverse effects on the mother or foetus. We aimed to assess the efficacy and safety of low-dose ketamine, used as an adjunct analgesic and amnesic, in attenuating the haemodynamic responses to laryngoscopy, intubation and surgery during caesarean section under general anaesthesia (GA). The occurrence of awareness based on clinical signs and the foetal outcome were also assessed.

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METHODS

This prospective, double blinded, randomised study was conducted from October 2012 to June 2015. Following approval from Hospital Ethical Committee, 40 consenting patients aged 18–45 years, with >36 weeks gestation, posted for elective caesarean section, who were not willing for regional anaesthesia, were studied. Exclusion criteria comprised of presence of maternal co-morbidities, foetal distress and patient refusal. The patients were randomly allotted to two groups by computer generated random sequence of numbers.

Following a thorough pre-anaesthetic evaluation, the patients were kept fasting for 8 h. The patients were premedicated with metoclopramide 10 mg and ranitidine 150 mg on the night prior to and on the morning of surgery. On arrival in the operation theatre, an 18 g cannula was inserted and lactated Ringer's solution was started and a wedge was kept under the right buttock. Pulse-oximeter, electrocardiogram and non-invasive blood pressure (NIBP) monitors were attached, and the abdomen was cleaned and draped.

Following 3 min pre-oxygenation, the study group (Group K) received 0.25 mg/kg body weight ketamine diluted to 5 ml, whereas the control group (Group C) received 5 ml normal saline intravenously (IV) just before induction of anaesthesia. All patients underwent rapid sequence induction with thiopentone 5 mg/kg followed by suxamethonium 2 mg/kg and were intubated with 6.5 or 7 mm cuffed endotracheal tube. After confirming correct tracheal placement of the tube, vecuronium 0.1 mg/kg was given IV, and patients were ventilated with oxygen and nitrous oxide mixture (40:60%) with 0.7% endtidal isoflurane maintaining normocarbia and normoxia. Following delivery of the baby, fentanyl 2 μ/kg and midazolam 2 mg were given IV and oxytocin 20 units in 500 ml Ringer lactate was started as an infusion.

Heart rate (HR), systolic and mean arterial pressures (MAP) were documented just before induction (baseline), then at 1, 3, 5, 7, 9, 12, 15, 20, 30 and 45 min after induction of anaesthesia. Patients were intubated immediately, following documentation of the haemodynamic parameters at 1 min after induction. Apgar score at 1 and 5 min after delivery were also documented. Gas analysis of umbilical vein blood was done and partial pressure of oxygen, carbon dioxide and pH were noted. Time taken from skin incision to delivery of the baby and time from uterine incision to delivery of the baby were also noted. Intraoperative lacrimation, if any, was noted.

Based on results of the previous study by Baraka *et al*.[3] on the changes in mean systolic blood pressure (SBP) (114 ± 9.0 vs. 127 ± 14), with 95% confidence and 90% power, minimum sample size was calculated to be 17 in each group to get statistically significant results. We used Mann–Whitney test to compare the demographics, HR, blood pressure, umbilical vein pH, pO_2, pCO_2, skin incision to delivery time, uterine incision to delivery time and the Apgar score between Group C and Group K. Fisher's exact test was applied to find the association of intraoperative lacrimation and hallucinations. Significance was assumed for $P < 0.05$.

RESULTS

The patients in both the groups were comparable with respect to the distribution of age, height, weight and American Society of Anesthesiologists physical status. The baseline HR, SBP and MAP of both the groups did not show any significant difference between the groups. The HR and SBP recorded 1 min after induction were comparable in both groups. However at 3, 5, 7, 9, 12, 15, 20, 30 and 45 min after induction, Group C showed a significantly high HR and SBP ($P < 0.05$) [Table 1, Figures 1 and 2]. The MAP at baseline, 1, 3 and 12 min in both the groups were comparable. At the same time, MAP at 5, 7, 9, 15, 20, 30, 45 min showed significant difference with Group C having higher values ($P < 0.05$) [Table 2].

In both Groups, the time taken from time of skin incision to delivery of baby (11.25 ± 2.38 and 11.30 ± 1.98 min) and the time for foetal delivery

Table 1: Comparison of mean heart rate (per min)

Time	Group C		Group K		*P*
	Mean	SD	Mean	SD	
Baseline	105.35	9.44	103.7	5.64	0.775
1 min after induction	114.75	11.08	108.65	6.1	0.078
3 min after induction	115.9	11.64	109.8	6.56	0.032
5 min after induction	112.8	11.65	103.9	6.56	0.003
7 min after induction	112	6.99	101.15	6.62	<0.001
9 min after induction	111.45	7.57	98.1	6.42	<0.001
12 min after induction	108.85	8.84	95.4	5.95	<0.001
15 min after induction	104.95	12.27	94.35	7.21	<0.001
20 min after induction	100.95	6.91	94.8	5.86	0.006
30 min after induction	99.45	6.29	93	5.66	0.001
45 min after induction	99.55	7.08	92.8	4.48	0.001

SD – Standard deviation

from the time of uterine incision (130.50 ± 36.49 and 112 ± 38.74 s) were comparable [Table 3]. Umbilical vein pO_2, pCO_2 and pH were also comparable in both the groups [Table 3, Figure 3]. Though Apgar score at 1 min showed a higher values in Group K, at 5 min both groups had comparable scores [Figure 3].

Higher number of the patients in Group C had intraoperative lacrimation as compared to Group K (50% vs. 0%, $P < 0.001$). Ten percent of the patients in Group C had hallucinations/recall of intraoperative events while none of the patients in Group K experienced the same, but the difference was statistically insignificant ($P = 0.487$).

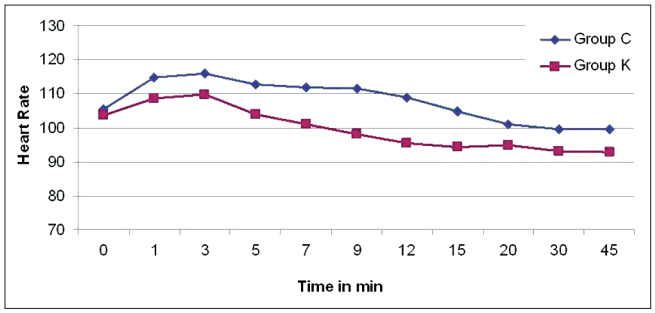

Figure 1: Changes in mean heart rate

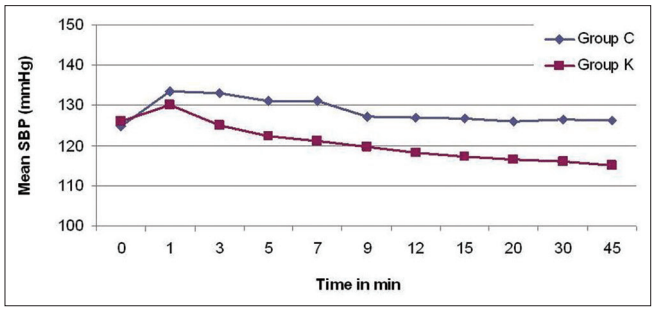

Figure 2: Changes in mean systolic blood pressure

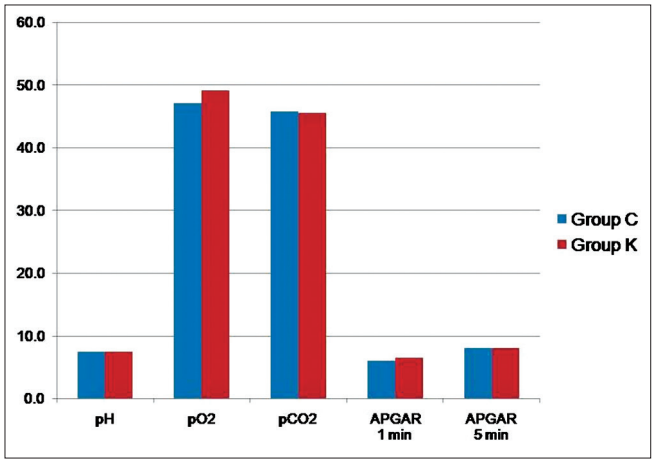

Figure 3: Comparison of umbilical vein blood gases and Apgar scores

DISCUSSION

Maternal hypotension and drug related foetal depression cause concerns in the practice of obstetric anaesthesia. However, regional anaesthesia remains the preferred choice in obstetric practice on account of its well established maternal and foetal benefits.[4]

The major indications for GA are foetal distress, abruption, eclampsia, uterine rupture and a prolonged and obstructed labour. Maternal refusal of regional techniques, inadequate regional block, or any contraindication for regional techniques such as coagulopathies or the presence of local infection may however necessitate administration of GA. The major concerns include difficulty in intubation, increased risk of aspiration, increased blood loss intraoperatively and development of awareness during anaesthesia.[5] Though GA is associated with a higher blood loss as compared to neuraxial anaesthesia, it is considered to be of uncertain clinical relevance.[6]

Apart from the added risks associated with physiological changes of pregnancy, the need to withhold sedatives and opioids until delivery of the baby to avoid foetal depression further complicates the

Table 2: Comparison of mean MAP at various time intervals (mm Hg)

Time	Group C		Group K		*P*
	Mean	SD	Mean	SD	
Baseline	92.9	10.46	94.58	6.5	0.607
1 min after induction	97.95	11.16	97.55	5.48	0.839
3 min after induction	96.3	10.56	95.28	9.44	0.386
5 min after induction	96.02	9.2	92.72	6.15	0.04
7 min after induction	95.4	7.41	91.72	5.38	0.02
9 min after induction	94.43	7.72	91.33	6.03	0.04
12 min after induction	93.38	7.64	90.48	7.36	0.093
15 min after induction	94.08	7.83	89.22	6.42	0.005
20 min after induction	94.98	5.4	88.88	8.47	0.003
30 min after induction	93.25	4.68	87.93	7.51	0.005
45 min after induction	93.38	3.28	87.85	5.7	<0.001

SD – Standard deviation; MAP – Mean arterial pressure

Table 3: Comparison of delivery time and foetal outcome

Variables	Mean±SD		*P*
	Group C	Group K	
Time			
Skin incision to delivery in min	11.25±2.38	11.30±1.98	0.77
Uterine incision to delivery in sec	130.50±36.49	112±38.74	0.104
Umbilical vein PO_2 (mm Hg)	47.05±3.80	49.15±5.62	0.135
Umbilical vein PCO_2 (mm Hg)	45.70±4.78	45.5±4.21	0.924
Umbilical vein pH	7.38±0.07	7.39±0.14	0.56

SD – Standard deviation; PO_2 – Partial pressure of oxygen; PCO_2 – Partial pressure of carbon dioxide

management of GA for caesarean section. Exaggerated haemodynamic responses are commonly observed at laryngoscopy, intubation and initial stages of surgery as the depth of anaesthesia will be less compared to other routine surgeries under GA.

The incidence of intraoperative awareness is more during caesarean sections under GA.[7,8] Ensuring an end-tidal concentration of volatile agent >0.8 MAC makes awareness unlikely.[9] However, the lack of availability of advanced respiratory gas monitors in many hospitals makes the accurate titration of the volatile agent concentration difficult. While the administration of high concentrations of volatile agents can result in postpartum haemorrhage, low concentrations result in exaggerated stress responses and awareness. The overwhelming concerns towards foetal well-being results in a tendency to use lower concentrations of volatile agents. This along with the practice of withholding opioids and benzodiazepines until foetal delivery could result in inadequate analgesia.

Quite often the only analgesic provided to these patients until the delivery of the baby is nitrous oxide alone, which is a poor analgesic. Along with a decrease in the volatile agents and analgesics, a higher oxygen concentration ($Fi0_2$ 0.5) is often used even though there is no rationale for an inspired oxygen concentration above 0.33 in the absence of foetal compromise.[10] This practice further reduces the analgesic effects of nitrous oxide. In the presence of foetal distress, even higher inspired concentrations of oxygen may be used.

In the present study, we used 0.7% isoflurane with 40% nitrous oxide in oxygen for maintenance of anaesthesia till delivery following the existing practice at our institute. We also aimed to assess the efficacy of our practice. We believed that an adequate depth of anaesthesia would be ensured with this concentration as it had been shown that use of 0.7% endtidal isoflurane along with 60% nitrous oxide provided one MAC in the age group of 20–30 years.[11]

Assessing depth of anaesthesia is challenging as clinical signs are unreliable and not specific. The clinical signs signalling development of awareness are mainly signs due to sympathetic stimulation. Intraoperative hypertension, tachycardia, lacrimation, sweating, coughing and patient movements could indicate development of awareness. BIS monitoring has been proven to be effective for monitoring depth of anaesthesia and scores <60 has been recommended to prevent the occurrence of awareness.[10] However, its availability and cost[8] limit its routine use.

As caesarean section is a commonly performed surgery, which is being performed even in hospitals with minimum monitors, BIS or auditory evoked potential index monitoring or even endtidal inhalation agent monitoring may not be available. Hence, a practical approach to minimize the problems of inadequate analgesia and awareness in these circumstances will be the use of analgesics with amnesic properties, with proven maternal and neonatal safety, from the beginning of surgery itself.

Ketamine is a time tested drug which provides good analgesia and amnesia. However, use of ketamine as a sole induction agent in caesarean section is not recommended as it causes significant maternal haemodynamic changes.[12] In addition, doses >1 mg/kg can theoretically increase uterine tone and jeopardise foetal circulation. However, these disadvantages could be overcome by careful dosing and by combining it with other drugs. It was shown that addition of a small dose of ketamine to thiopentone for induction provided reduced analgesic requirement without side effects and was found not to affect maternal or foetal well-being.[12]

It has been shown that ketamine when given along with propofol can reduce the hypotensive effects of propofol.[13,14] Used as an adjunct in doses of 1 mg/kg, 0.5 mg/kg and 0.25 mg/kg, ketamine had resulted in comparable maternal intraoperative haemodynamic parameters, Apgar scores and post-operative analgesia.[15] A single bolus dose of ketamine was found to decrease post-operative opioid requirements, and adverse effects were not increased with low-dose ketamine. Hence, low-dose ketamine has been recommended as a safe and useful adjuvant to standard practice opioid-analgesia.[16] The advantage of using lower doses of ketamine is that the incidence of adverse effects can be reduced. Prophylactic IV ketamine 0.25 mg/kg was found to be effective in preventing intraoperative shivering during caesarean sections under subarachnoid block.[17]

In our study, patients were intubated immediately after documenting the haemodynamic parameters at 1 min following induction. Therefore, the haemodynamic parameters recorded at this point did not reflect the intubation response. In fact, the haemodynamic

parameters recorded following laryngoscopy and intubation actually correspond to the values recorded at 3 min after induction and later. The time interval for NIBP measurements was set at 2 min in the initial period so as to minimise distraction of the anaesthesiologist. Hence, the haemodynamic parameters immediately following intubation were not recorded. The blunted haemodynamic responses observed from 3 min onwards extending throughout the study period indicate that ketamine 0.25 mg/kg effectively attenuated the stress response to laryngoscopy, intubation and surgery. This could be attributed to the additional analgesia and/or amnesia provided by ketamine.

The umbilical vein blood gas analysis and Apgar score reflect adequacy of the uteroplacental circulation. Better Apgar scores observed in ketamine group at 1 min in our study could be because of the attenuated stress response to laryngoscopy, intubation and surgery. As the sympathetic stimulation was less intense in this group, it could have resulted in lower plasma catecholamine levels, less vasoconstriction and normal placental perfusion. Though statistically insignificant, the higher mean PO_2 and lower mean PCO_2 observed in the ketamine group support this [Table 3].

The main disadvantage of our study was that our observations were linked to the clinical signs for detection of the development of awareness. Though intraoperative lacrimation/tachycardia/hypertension could reflect development of awareness, these signs are not specific. The availability of BIS monitoring would have provided more reliable information on the depth of anaesthesia. However, the addition of low dose ketamine to the general anaesthetic regimen can still be considered for reducing the occurrence of intraoperative awareness.

CONCLUSION

IV ketamine 0.25 mg/kg, when used as an adjunct analgesic and amnesic, attenuates the haemodynamic responses during caesarean section under GA without affecting the foetal outcome.

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Conflicts of interest
There are no conflicts of interest.

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