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EFFICACY AND SAFETY OF LOW DOSE KETAMINE AS AN ADJUNCT ANALGESIC IN CAESAREAN SECTION UNDER GENERAL ANESTHESIA

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ABSTRACT

Background and aims: The practice of avoiding sedatives or anxiolytics in caesarean section under general anesthesia (GA) until delivery of the baby could result in exaggerated hemodynamic 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, randomized double blinded study was conducted in 60 patients. Group K (n = 30) received 0.25 mg/kg ketamine, whereas Group C (n=30) received 5 ml normal saline intravenously (IV) just before induction of anaesthesia. After intubation, patients were ventilated with O2 and N2O (33% : 66%) with 0.7% isoflurane. Fentanyl and midazolam were given following delivery of the baby. Chi square test and student T test were used for statistical analysis.

Results: Pre -induction hemodynamic parameters and those recorded at 1 min after induction were comparable in both groups. However, heart rate systolic blood pressure and mean arterial pressure (at 3, 5, 7, 9, 12, 15, 20, 30 and 45 minutes after induction) showed significantly high values in Group C ($P < 0.05$). Apgar score at 1 min, and at 5 min in both the groups had comparable scores. In Group C, intraoperative lacrimation (57 vs.1 0%) and recall of intraoperative events (17 vs. 3%) were high.

Conclusion: IV ketamine 0.25 mg/kg can be safely used as an adjunct analgesic and amnesic to attenuate hemodynamic responses during caesarean section under GA without affecting the foetal outcome.

KEYWORDS : Awareness, Caesarean section, General anaesthesia, Ketamine.

INTRODUCTION

The risks of exaggerated hemodynamic responses &awareness during General anaesthesia and surgery 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 hemodynamic responses and monitoring indices, such as the bispectral index (BIS) and auditory evoked potential index, 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 hemodynamic 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.

MATERIALS AND METHODS

This double – blinded, prospective, randomized control study was performed after obtaining approval from the institutional ethical committee. The study was conducted in 60 consenting patients, aged between 20 to 35 years, with uncomplicated singleton pregnancy. Any contraindication for general anesthesia, maternal comorbidities, foetal distress and patient refusal were excluded from this study.

They were randomly allocated into following groups. Group C patients received 5 ml of normal saline (placebo). Group K received Inj.Ketamine 0.25mg/kg diluted to 5ml with distilled water just before induction of general anaesthesia.

Randomization was performed using a computer – based random number generator in permutated blocks of different sizes and the assignment was entered in sealed covers that were not opened till informed consent was obtained.

The study was a double blinded one, where the anesthesiologist or the data collector who involved in this study and the patients were blinded to the assignment groups. The syringes were prepared by the anesthesiologists who were not involved in this study.

PREOPERATIVE PREPARATION

Patients were kept fasting overnight and oral metoclopropamide 10 mg and oral ranitidine 150 mg were given on the night prior to and on the morning of the day of surgery.

After routine preoperative assessment at the patients waiting room in the OT, baseline readings of the vital parameters were recorded. Intravenous line started and lactated ringer solution started. Patients were randomly allocated into two groups of 30 each by using closed cover technique.

Preoperative baseline HR, Systolic blood pressure, Mean arterial pressure were noted using multipara monitor and a wedge was placed under the right buttock.

Following three minutes of pre-oxygenation, according to random ization (closed cover technique) the patients received either 5 ml of normal saline or Inj.Ketamine 0.25 mg/kg diluted in 5 ml distilled water(30-45 Seconds) just before induction of anaesthesia.

All patients underwent rapid sequence induction with thiopentone 5-7 mg/kg and suxamethonium 1-1.5 mg/kg and intubated with 6.5 or 7mm cuffed endotracheal tube.

After confirming correct tracheal placement of the tube, vecuronium 0.1 mg/kg was given iv and the patients were ventilated with N2O:O2 = 66% : 33 %and 0.7 % Isoflurane.

Following delivery of the baby, fentanyl 2 µg/kg and midazolam 0.5mg/kg were given IV and oxytocin 20 units in 500ml of ringer lactate solution started as an infusion.

The following parameters were noted

1. HR, SBP, MAP at baseline (just before induction) and then at 1 ,3, 5, 7,9,12 ,15 ,20, 30, 45 minutes after induction.
2. APGAR score 1 and 5 minutes.
3. Time taken from skin incision to baby delivery(I-D interval).
4. Time taken from uterine incision to baby delivery(U-D interval).
5. Intraoperative lacrimation.
6. Recall of intraoperative events.

7. Occurrence of any complications.

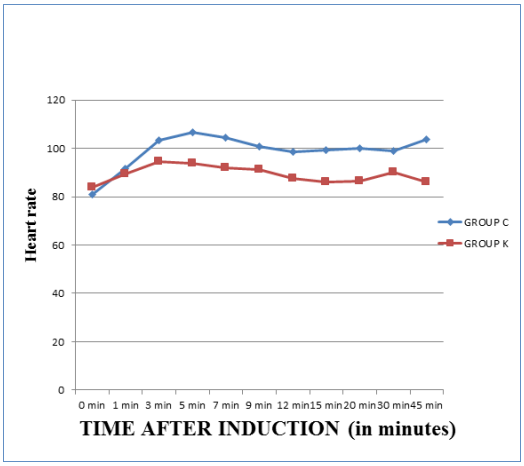
OBSERVATIONS AND RESULTS

All 60 patients in two groups completed the study without any exclusion. we did inter group analysis and the results were as followed. The collected data was analyzed using Chi square test, student T test and the probability value ' p'< 0.05 was considered as statistically significant.

There is no difference in age between the two groups and they were comparable statistically.

TABLE 1
MEAN HEART RATE COMPARISION BETWEEN THE GROUPS

TIME	GROUP C (Mean ± SD)	GROUP K (Mean ± SD)	P VALUE
Baseline	80.90 ± 9.81	83.17 ± 9.06	0.356
1 minute after induction	91.70 ± 11.21	89.23 ± 9.68	0.356
3 minute after induction	103.23 ±12.41	94.33 ± 9.31	0.003
5 minute after induction	106.07 ± 10.63	93.77 ± 10.96	< 0.001
7 minute after induction	104.43 ± 8.55	91.87 ± 10.48	< 0.001
9 minute after induction	100.87 ± 8.85	91.13 ± 9.36	< 0.001
12 minute after induction	98.63 ± 8.52	87.43 ± 9.77	< 0.001
15 minute after induction	99.33 ± 11.36	85.93 ± 10.49	< 0.001
20 minute after induction	100.20 ± 8.91	86.40 ± 9.34	< 0.001
30 minute after induction	98.93 ± 10.26	89.97 ± 6.86	< 0.001
45 minute after induction	103.70 ± 11.66	86.00 ± 8.06	< 0.001



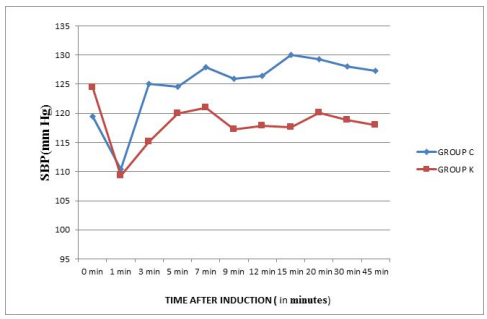
GRAPH 1: MEAN CHANGES IN MEAN HEART RATE

Heart rate was monitored from preoperative baseline to 45 minutes after induction (11 intervals), and there is no statistical difference between the two groups at 0 min (p value is 0.356). and at 1 min (p value is 0.365).

In Group K patients the mean heart rate at 3,5,7,9,12,15,20,30,45 minutes after induction is lower than the Group C patients and is statistically significant. The p value at 3 ,5 ,7,9 ,12,15,20,30,45,minute after induction were less than 0.001 and is very highly significant statistically.

TABLE 2
COMPARISION OF SYSTOLIC BLOOD PRESSURE AT VARIOUS TIME INTERVAL BETWEEN THE TWO GROUPS (mm Hg)

TIME	GROUP C (Mean ± SD)	GROUP K (Mean ± SD)	P VALUE
Base line	119.50 ± 8.61	124.40 ± 8.73	0.33
1 min after induction	110.37 ± 8.39	109.33 ± 8.09	0.629
3 min after induction	125.00 ± 11.12	115.13 ± 8.80	**< 0.001**
5 min after induction	124.57 ± 8.74	120.03 ± 9.46	0.059
7 min after induction	127.87 ± 7.56	120.97 ± 10.02	**0.004**
9 min after induction	125.93 ± 7.32	117.20 ± 9.63	**< 0.001**
12 min after induction	126.40 ± 8.22	117.87 ± 11.86	**0.002**
15 min after induction	129.97 ± 8.04	117.63 ± 11.52	**< 0.001**
20 min after induction	129.33 ± 7.29	120.13 ± 9.07	**< 0.001**
30 min after induction	128.07 ± 6.66	118.83 ± 9.65	**< 0.001**
45 min after induction	127.30 ± 6.56	117.97 ± 8.57	**< 0.001**



GRAPH 2: CHANGES IN SYSTOLIC BP BETWEEN THE TWO GROUPS

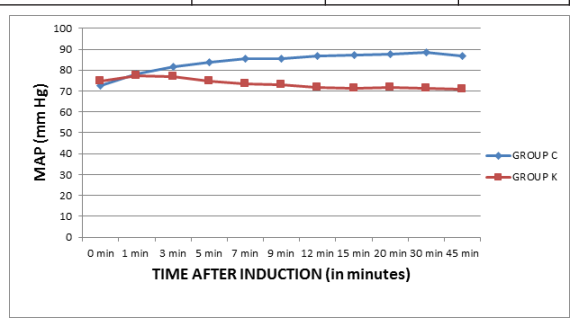
In both the groups systolic blood pressure measurements at baseline & at 1 min were comparable. There was no statistically significant difference

(p 0.05). Systolic blood pressure observations shows that there is no statistical significant difference in between the groups at 0,1,5 minutes after induction, but in Group K patients, the measurements are significantly lower when compared to group C patients & there was a statistically, very high significant difference in between the groups at 3,7,9,12,15,20,30,45 minutes after induction of anaesthesia

(p< 0.001).

Table 3: COMPARISION OF MEAN ARTERIAL PRESSURE BETWEEN THE TWO GROUPS

TIME	GROUP C (Mean ± SD)	GROUP K (Mean ± SD)	P VALUE
Baseline	72.43 ± 4.98	74.83 ± 5.18	0.072
1 min after induction	78.10 ± 7.91	77.43 ± 6.51	0.723
3 min after induction	81.53 ± 6.73	76.80 ± 5.57	**0.004**
5 min after induction	83.90 ± 7.04	74.83 ± 4.36	**< 0.001**
7 min after induction	85.33 ± 6.02	73.37 ± 5.56	**< 0.001**
9 min after induction	85.37 ± 7.69	72.87 ± 4.84	**< 0.001**
12 min after induction	86.77 ± 8.19	71.83 ± 3.94	**< 0.001**
15 min after induction	87.03 ± 8.90	71.23 ± 3.96	**< 0.001**
20 min after induction	87.67 ± 9.48	71.53 ± 3.88	**< 0.001**
30 min after induction	88.60 ± 9.08	71.27 ± 4.02	**< 0.001**
45 min after induction	86.73 ± 10.92	70.83 ± 3.48	**< 0.001**



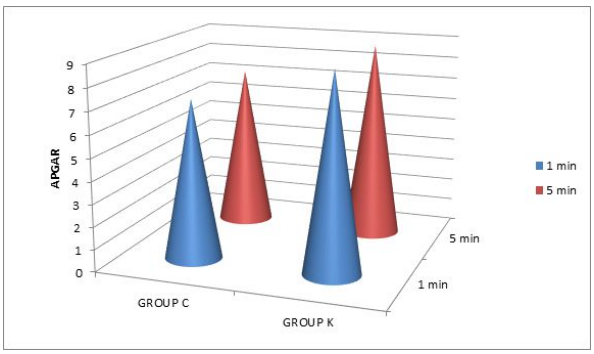
GRAPH 3: CHANGES IN MEAN ARTERIAL PRESSURE BETWEEN THE TWO GROUPS

The mean MAP was comparable between both the groups at 0 and 1 minute following induction. There was no statistically significant difference among the two groups at 1 minute and 5 minutes of induction.(P > 0.05)

In Group K, MAP was significantly lower when compared to Group C. There was a very high statistically significant difference between the two groups at 3, 5,7,9,12,15,20,30,45,minutes after induction. (P < 0.001)

TABLE 4 COMPARISION OF MEAN APGAR SCORE BETWEEN THE TWO GROUPS:

TIME	GROUP C (Mean±SD)	GROUP K (Mean±SD)	P VALUE
1 minute	7.17 ± 0.64	7.30 ± 0.46	0.364
5 minutes	8.87 ± 0.34	8.87 ± 0.34	1.000



GRAPH 4 : APGAR SCORE COMPARISON

Apgar values between the two groups were comparable . There was no statistically significant difference between the two groups at both 1 minute and at 5 minutes. (P > 0.05)

I-D interval does not show any statistically significant difference between the two groups, (p > 0.05)

U-D interval does not show any statistically significant difference between the two groups, (p > 0.05)

Introperative lacrimation is one of the clinical sign of awareness and is present in 17 out of 30 patients in Group C. Group K patients had 3 out of 30 patients. There is a very high statistically significant difference between the two groups (p < 0.001).

In Group C, 5 out of 30 patients experienced recall of intraoperative events and in Group K , only 1 patient out of 30 had recall of intraoperative events. since the p value is 0.085, there is no statistically significant difference .

DISCUSSION

Caesarean section under GA is a major risk factor for intraoperative awareness due to the practice of avoidance of sedatives and anxiolytics till the delivery of the baby. The lack of advanced respiratory gas monitors in many hospitals make the accurate titration of volatile agent concentration difficult .Isoflurane can be safely administered in pregnancy without affecting the neonate according to **Piggot SE et al (6)**

The overwhelming concerns towards the fetal well being tends to use lower concentrations of volatile agents. Thi0s along with the practice of withholding opioids and benzodiazepines until fetal delivery could result in inadequate analgesia . Most often , the only analgesics provided to these patients until the delivery of the baby is N2O alone , which a poor analgesic .In our study , we used 0.7% isoflurane with N2O : O2 = 66% :33% for maintenance of anaesthesia till delivery . In a study conducted by **Nickfalls et al (5)** it was shown that 0.7 % end tidal isoflurane along with 60% N2O provided 1 MAC in the age group of 20 to 30 years.BIS monitoring is effective in monitoring the depth of anaesthesia and depth scores < 60 has been recommended to prevent the occurrence of awareness . **(Robins K et al) (7)**

In our hospital setting , without BIS monitoring or auditory evoked potential index monitoring , the use of analgesic with amnesic property from the start of the surgery itself is a practical approach to minimize the inadequate analgesia and awareness .Hence we chose ketamine , a good analgesic and amnesic, and clinical signs for awareness monitoring .

In a study conducted by **Nayar R et al (4),** they concluded that the addition of ketamine in low doses to thiopentone for induction leads to reduced analgesic requirements without side effects and without affecting maternal or fetal well being. In a study done by Traub **E et al (11)**, they found that ketamine induction can be safely done in caesarean section. Hence we chose Inj.Ketamine 0.25mg/kg iv before induction in our study .

In our study the patient's ages are comparable between the two groups The results of the present clinical study are discussed under the following headings.

- Heart rate, Systolic blood pressure,
- Mean arterial pressure
- Apgar score at 1 and 5 minutes.
- Skin incision to baby delivery interval.
- Uterine incision to baby delivery interval.
- Intraoperative lacrimation.
- Recall of intraoperative events.

HEART RATE:

In our study we heart rate were recorded just before induction (baseline) and then at 1,3,5,7,9,12,15,20,30,45 minutes after induction. Heart rate recorded at baseline (p-0.356) and at 1 min (p-0.356) doesn't show any statistical significant difference between the two groups. However in Group K, heart rate recorded at 3,5, 7,9,12,15,20,30,45 minutes after induction is significantly lower than Group C (p < 0.05). In a study conducted by **Sunil Rajan et al (10)**, they concluded that Ketamine 0.25mg/kg effectively attenuated the stress response to Laryngoscopy, intubation and surgery which could be attributed to the additional analgesia and amnesia provided by ketamine. Our study also concurs with studies conducted by **Nayar R et al (4), Bilgen S et al (1), Schultetus et al (1986) (8),**

SYSTOLIC BLOOD PRESSURE:

In our study, Systolic blood pressure was monitored at baseline and at 1,3 ,5,7,9,12,15,20,30,45 minutes after induction. Systolic blood pressure recorded at baseline (p-0.33) ,1 min (p-0.629) and 5 min (p-0.059), doesn't show any statistical significant difference between the two groups. However in Group K, SBP values recorded 3mins (p < 0.05) after induction was significantly lower than Group C. **Sunil Rajan et al(10)**, also observed a similar decrease in Systolic blood pressure after 3 minutes of induction except at 5 mins..

Our study shows similar results when compared to other studies conducted by **Nayar R et al (4), Bilgen S et al (1), Schultetus et al (9)**.

MEAN ARTERIAL PRESSURE:

In our study, Mean arterial pressure was monitored at baseline and at 1,3 ,5 ,7 , 9, 12 , 15 , 20, 30 ,45 minutes after induction. Mean arterial pressure recorded at baseline(p-0.072) and at 1 min(p-0.723) doesn't show any statistical significant difference between the two groups. However in Group K, SBP values recorded after 3mins of induction were significantly lower than Group C, (p < 0.001).This observation concurs with the study done by **Sunil Rajan et al (10) . Nayar R et al (4), Bilgen S et al (1), Schultetus et al (9),**

APGAR

APGAR scores at 1 min (p-0.364) and 5 min (p-1.000) does not significantly differ in both the groups. **Nayar R et al (4), Schultetus et al (9)** also concluded that ketamine 0.5mg per kg when combined with thiopentone for induction, did not affect the neonatal outcome .

According to **Downing J W et al (3)** when ketamine 2mg/kg is used for induction of anesthesia in caesarean section, may account for drug induced neonatal depression and hence ketamine should be reevaluated at a lower dose. That's why we choose ketamine in a lower dose.

SKIN INCISION TO BABY DELIVERY INTERVAL

The ID interval is measured to evaluate the effect of ketamine on the

muscle tone.

The use of ketamine in dose of 0.25 mg/kg does not affect the muscle tone and there was no statistically significant difference between the groups (P value 0.085). The mean I-D interval in our study is in group K is 9.13±1.655. **Bernstein k et al (2)**, also observed similar results.

UTERINE INCISION TO BABY DELIVERY INTERVAL

The U-D interval in our study group is not significantly different than the control group (P - 0.255).This is in concordance with the study conducted by **Sunil Rajan et al (10).**

INTRAOPERATIVE LACRIMATION

There is a significant decrease in the occurrence of intraoperative lacrimation in the ketamine group in our study when compared to the control group (P < 0.001).

RECALL OF INTRAOPERATIVE EVENTS

Recall of intraoperative events occurred in 5 out of 30 patients in Group C and 1 out of 30 in Group K, but the difference was not statistically significant (P - 0.085).

LIMITATIONS OF THE STUDY

1. The umbilical venous blood gas analysis and maternal blood gas analysis could not be done in our institution, we used the APGAR score for monitoring of neonatal outcome .
2. The main disadvantage of our study was that our observations were made based on the clinical signs of awareness, because of the unavailability of BIS monitoring in our institution.
3. As respiratory gas monitor is not available in our institution, we could not monitor end tidal concentration of Isoflurane.

CONCLUSION

IV ketamine when used as an adjunct analgesic and amnesic in a dose of 0.25mg /kg just before induction of GA in elective caesarean section, attenuates the hemodynamic responses and awareness, without affecting the neonatal outcome.

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