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Evaluating Effect of Intraoperative Infusion of Low Dose Ketamine on Hemodynamics and Postoperative Pain amongst Patients Undergoing Abdominal Surgery under General Anesthesia; A Prospective Observation Study

Dr. Arshiya I Shaikh[1], Dr. Jignasa J Patel[2], Dr. Neelam Parmar[3], Dr. Tejal A Chaudhari[4]

[1]Third Year Post Graduate Resident, Department of Anesthesiology, Government Medical College, Surat, Gujarat, India

[2]Assistant Professor, Department of Anesthesiology, Government Medical College, Surat, Gujarat, India
Corresponding author Email: *jignasa72[at]gmail.com*
Phone (or Mobile) No: 9924177720

[3]Assistant Professor, Department of Anesthesiology, Government Medical College, Surat, Gujarat, India

[4]Assistant Professor, Department of Anesthesiology, Government Medical College, Surat, Gujarat, India

Abstract: ***Background: Major abdominal surgeries are associated with large fluid shifts and blood loss intra-operatively and significant pain postoperatively. Ketamine has unique sympathomimetic property, opioid sparing effect and intense analgesic property even in subanesthetic dose. So, this study was planned to evaluate the effect of low dose ketamine infusion on intraoperative hemodynamics, opioid requirements and postoperative pain. Method: A prospective observational comparative study was conducted on 60 patients of either sex in age group of 18 - 60 years belonging to ASA class III and IV. GA was given with STP, scoline, vecuronium/atracurium and sevoflurane. 30 patients in Group K received injection Ketamine 0.5 mg/kg bolus followed by 0.25 mg/kg infusion while 30 patients in Group C did not received Ketamine. Intraoperative hemodynamic parameter and opioid requirement were noted. Postoperative quality of pain was evaluated through VAS score up to 12 hours. First rescue analgesic time, cumulative tramadol consumption, total number of doses of rescue analgesics within 12 hours and side effects were noted. Results: The mean age, mean weight and mean duration of surgery were comparable between both the groups (P>0.05). Intergroup comparison of mean preoperative pulse rate and mean preoperative blood pressure was comparable (P>0.05), intragroup comparison of intraoperative hemodynamics was more stable in ketamine group when compared to baseline. Postoperative mean VAS score difference was statistically significant for first 3 hours (P<0.05). First rescue analgesic requirement was 222 minutes in Group K and 110 minutes in Group C (P=0.014). 26% of patient in Group K and 63% of patients in Group C required ≥ 2 doses of tramadol postoperatively. Cumulative tramadol requirement was more in Group C as compared to Group K (193.33 ± 90.17 mg VS 286.6 ± 84.4 mg, P = 0.002). 43% patients in Group K had an emergence reaction which were treated with an incremental dose of midazolam. The required mean dose of midazolam was 1.11 mg. Conclusion: Intraoperative low dose ketamine infusion provides stable intraoperative hemodynamics and perioperative analgesia, with its potent opioid sparing effect and it should be considered as an effective and safe component of multimodal analgesia.***

Keywords: ketamine, subanesthetic dose, hemodynamics, Fentanyl, postoperative pain

1. Introduction

Ketamine is a N-Methyl-D-Aspartate (NMDA) receptor antagonist, provides dissociative anesthesia, it exerts its effect by acting on NMDA, opioid and Monoamine oxidase receptors.(1) Ketamine has analgesic, hypnotic and amnesic effects.(2) Ketamine has dual effect on cardiovascular system; direct cardio depressive negative ionotropic effect next to an indirect stimulatory effect due to activation of the sympathetic system.(3)

Recently, interest in ketamine has increased due to its excellent analgesic effect even at low dose and its effect on hyperalgesia and opiate tolerance;its use in chronic pain states and having a neuroprotective effect.

Major abdominal surgery is associated with large fluid shifts and blood loss intraoperatively and significant pain postoperatively, because of large incision, extensive tissue dissection and manipulation of viscera.Therefore, prime anesthetic concern during major abdominal surgery is the fluid management and maintenance of stable hemodynamics by proper fluid management, intraoperatively and adequate postoperative pain management.

As ketamine has a unique symapathomimetic property, it can help in maintenance of stable hemodynamics in this kind of high risk patients in which we expect hypotension intraoperatively. It has opioid sparing effect by which it reduces the requirement of opioid and also prevent the development of opioid induced hyperalgesia.

Literature shows that even in (sub-anesthetic) dose ketamine holds its analgesic property and its analgesic effect outlast its duration of anesthesia and at these doses the psychomimetic adverse effects of ketamine are infrequent.

Very few studies have been conducted to evaluate the effect of low dose ketamine infusion on hemodynamic parameters. So, we planned this study to evaluate the effect of intraoperative low dose ketamine infusion on hemodynamics, intraoperative opioid requirements and postoperative pain.

2. Material and Method

After approval from ethical committee, this observational prospective study was conducted on 60 adult patients in age group of 18 to 65 year scheduled for planned abdominal surgical procedures having a duration of ≥ 2 hour, Belonging to ASA class III and IV, to evaluate the effect of intraoperative infusion of low dose ketamine on hemodynamic, opioid consumption and postoperative pain. Patients with hypertension, IHD, increased ICP, thyrotoxicosis and psychiatric illness were excluded from the study.

A detailed pre anesthetic check-up was done a day before surgery and patients were explained about Visual Analogue Scale score (VAS) of 0-10 with 0 being "no pain" 10 being "worst possible pain". Procedure to be performed was explained to patient and patient's relatives and written informed consent was taken on the day of surgery. All patients were kept nil by mouth for atleast 6 hours.

On the day of surgery, in preoperative room patient's baseline pulse rate, BP and SPO2 were noted and 20G or 18G intravenous canula was secured and IV fluid was started. All patients were premedicated with Inj. Glycopyrrolate 0.2 mg/kg, Inj. Ondansetron 0.1 mg/kg, Inj. Midazolam 1 mg and Inj. Tramadol 100 mg intravenously 20 minutes before induction.

After shifting patient to operation theatre, NIBP, pulse oximeter, ECG monitoring were attached and above mention parameters were noted.

According to standard protocol, all patients were induced with Inj. STP (2.5%) 4-7 mg/kg and Intubation was facilitated by Inj. Scoline 2 mg/kg intravenously. Anesthesia was maintained with O2 (50%) + N2O (50%) + inhalational Sevoflurane + NMDR (Vecuronim/Atracurim). Parameters like Pulse rate, Systolic BP, Diastolic BP, Mean Arterial Pressure, SPO2 were monitored at regular intervals.

Patients who received Ketamine (bolus 0.5 mg/kg followed by infusion 0.25 mg/kg/hr) intraoperatively throughout the surgery were included in Ketamine Group K and patient who did not receive Ketamine infusion formed the Control Group.

Ketamine infusion was discontinued at the initiation of wound closure. Hemodynamic parameter (pulse and BP) beyond the range of 20% from the baseline was considered significant; If hypotension episode is there it was treated with: Intravenous fluid or inj. Ephedrine 0.6mg or vasopressors, In case of bradycardia, patients received injection atropine 0.6 mg iv bolus and If hypertension and tachycardia had occur patients received Inj. Fentanyl 100mcg.

Intraoperatively total requirements of Opioid were noted. At the end of surgery, Inj. Paracetamol 1gm. IV was given. Residual neuromuscular blockade was reversed with Inj. Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 0.04mg/kg. After reversal patient was assessed for pain using VAS at regular interval of 30 minutes up to 2 hours and then at 3hr, 6hr and 12hr.If VAS ≥4, then Inj. Tramadol 100mg was given, intravenously as rescue analgesic. Total requirement of analgesic agents was noted up to 12 hours.

In Post anesthesia Care Unit, patients were observed for emergence reaction and other side effects like sedation, nausea, vomiting and respiratory depression. If emergence reaction occurred Inj. Midazolam 1mg intravenously was given and If needed 1 mg was repeated and total requirement was noted. Patients were kept in PACU for 3 hours.

Convenient sample technique was use to determine sample size and statistical analysis was done using SPSS version 18.0 using student's t test, Chi-Square Test, Mann Whitney U Test. The difference was considered to be statistically Significant when $P < 0.05$, highly significant when $P \leq 0.001$, and extremely significant when $P \leq 0.0001$.

3. Observation and Results

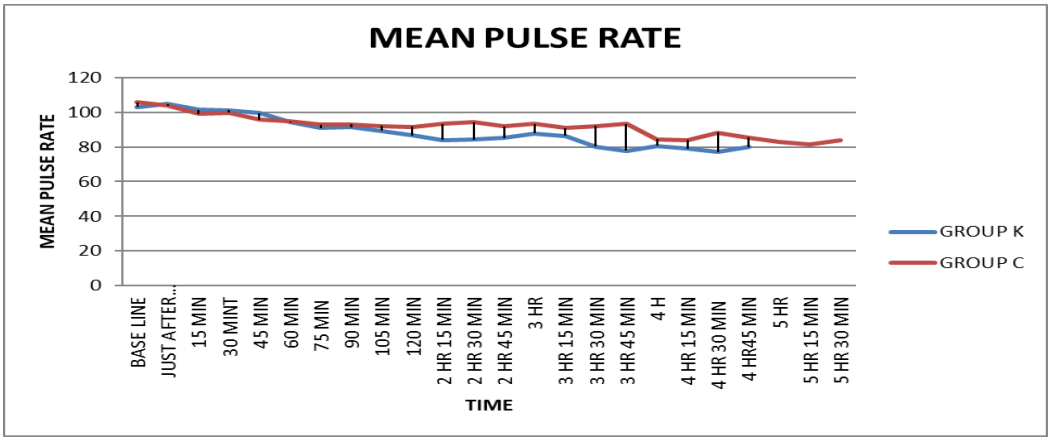
A comparative observational cohort study was conducted to evaluate the effect of intraoperative low dose ketamine infusion on intraoperative hemodynamics and post operative analgesia at tertiary care center during period of June 2021-September 2022.

Mean age of patients in Group K was 37.1 ± 12.7 years and in group C was 38.9 ± 14.8 years and the mean weight of patients in group K 48.4 ± 8.6 kg and in group C was 52.3 ±12 kg. Thus, mean age and mean weight was comparable between both the groups (P>0.05).

The mean duration of surgery was comparable between both the groups (P>0.05); 184.5 ± 456 mins in Group K and 181 ± 49.8 mins in Group C.

Inter group comparison of the preoperative pulse rate and mean MAP before induction were comparable between two groups (P>0.05). The pulse rate of Group K was 92.6±16.44 beats/ mints and in Group C it was 89±16.02 beats/ mints. The preoperative mean MAP in Group K was 88.9 ± 11.09 mm hg where as in Group C it was 89.23 ± 11.6 mm hg.

Intragroup comparison was also done and the mean intraoperative pulse rate and MAP was compared with base line pulse rate and MAP in both the groups.



Graph 1: Mean Pulse Rate at Various Intervals (N=60)

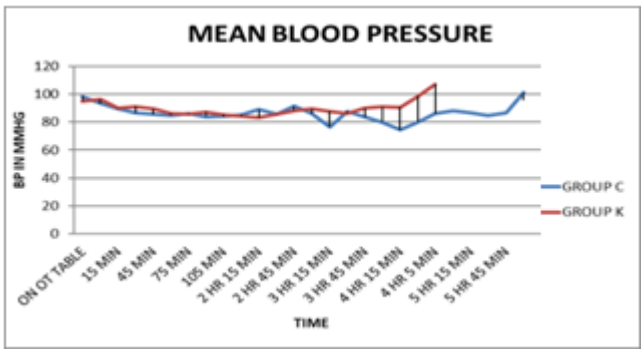
The above graphs show trend of mean pulse rate of both the groups.

In Group K, there was statistically significant (P<0.05) difference in mean pulse rate (i.e. pulse rate was reduced from baseline value) after 60 minutes of surgery and remained so throughout the surgery (from which at 2 hour, 2 hour 15 mintues, 2 hour 30 minutes,3 hour 30 minutes and at 3 hour 45 minutes, difference was highly significant i.e. P<0.001). Clinical significance was considered if the mean heart rate was beyond the range of 20% from baseline value. The mean pulse rate was significantly reduced at 3 hour 30 minutes and remained so throughout the surgery in Group K and it was not clinically significant.

In Group C, there was no significant difference statically in mean pulse rate (P > 0.05) at just after induction, 15 minutes ,2 hour 45 minutes,3 hour 45 minutes, 4 hours 30 minutes, 5 hours, 5 hours 30 minute and just after extubation. In remaning period of time, the difference was statistically significant i.e. pulse rate was reduced from base line (P<0.05). Clinically, in Group C mean baseline pulse rate was reduced significantly at 5 hr, 5 hr 15 mins and 5 hr 45 mins.

The intergroup comparison of mean heart rate shows that the difference was statistically insignificant throughout the surgery (P>0.05).

None of the patients in both the groups had bradycardia and required inj. Atropine.



Graph 2: Mean BP at various intervals

The above graph shows trend of mean MAP of both the groups.

In Group K, mean arterial blood pressure difference was statistically significant from 60 mints to 2 hr 30 mints (P<0.05) and rest of the time mean arterial blood pressure difference was statistically not significant (P>0.05).

As the MAP remained within the range of 20% from baseline, throughout the surgery, the difference was clinically non- significant.

In Group C mean arterial blood pressure difference was not statistically significant when compared to baseline at 15 mints,90 mints, 105 mints, 2 hr 45 mints and 4 hr 45 mints onward and remained so throughout the study period (P>0.05). At rest of the time period, it was statistically significant (P<0.05), from which at 45 mints,120 mints, 3 hr 15 mints and at 4 hr 15 mints it was highly significant (P<0.001), mean arterial blood pressure was significantly decreased clinically at 3 hr 15 mints and 4 hr 15 mints [as this difference was more than 20%]. We found stable hemodynamics in ketamine group and compared to the control group.

In Group C, mean arterial blood pressure was significantly decreased clinically at 3 hr 15 mints and 4 hr 15 mints. [as this difference was more than 20%]

The intergroup comparison of mean arterial blood pressure showed no clinical as well as statistical significance throughout the study period (P>0.05). Inj. Fentanyl 2 mcg/kg was supplemented when HR and MAP were >20% of baseline. In Group K, 26% of the patients required fentanyl compared to Group C, in which 43% patients required Fentanyl. Thus, it was statistically significant(P=0.04.

Table 1: Mean VAS at various interval (N=60)

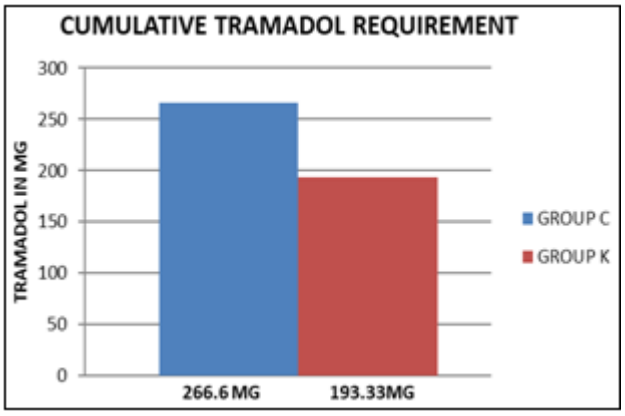
	Group K (N=30)		Group C (N=30)		P Value
	Mean	SD	Mean	SD	
Just After Extubation	0.47	1.07	0.83	1.02	<0.05(0.03)
30 MIN	1.5	1.5	2.5	1.33	<0.05(0.008)
60 MIN	2	1.23	3.2	1.21	<0.001(0.0004)
90 MIN	2.6	1.37	3.03	0.96	<0.05(0.04)
120 MIN	3.03	1.15	3.87	1.45	<0.05(0.02)
180 MIN	3.23	1.13	4.13	1.25	<0.05(0.005)
6 HR	3.63	0.89	3.83	1.2	>0.05(0.5)
12 HR	3.93	1.05	4.27	1.14	>0.05(0.2)

The mean VAS score at various interval were compared for 12 hours postoperatively, there was statistically significant difference in VAS score just after extubation to period of 3 hours post operatively (P<0.05) from which at 60 minutes; it was highly significant (P<0.001, P=0.0004). At 6 hour and 12 hours interval VAS score showed no significant difference between the two groups.

If VAS score was ≥4, Inj. Tramadol 100 mg was given.

Mean time of first rescue analgesic request was prolonged in Group K, it was 222 minutes while in Group C, it was 110 minutes. Thus, it was statistically significant (P<0.05, P=0.014).

In Group K, 26% of patients required more than 2 doses of rescue analgesia, while in Group C it was 63% who required more than 2 doses of Tramadol.



Graph 3: Mean Cumulative Tramadol Requirement

The cumulative tramadol requirement was more in Group C compared to Group K within 12 hours postoperatively and was statistically significant (P<0.05, P=0.002), (266.6 ± 84.4 mg VS 193.33 ± 90.71 mg).

In Group K, 43% of patients had an emergence reaction and it was treated with Inj. Midazolam in incremental dose.

Mean requirement of midazolam in Mg was 1.11 mg in group K.

4. Discussion

Major abdominal surgeries like gastrectomy, esophagectomy, (Resection – anastomosis) hemicolectomy, esophagectomy, etc. are associated with major fluid shift as well as electrolyte imbalance preoperatively and intraoperatively. So, these patients are more prone for hypotension.

Two main concerns to the anesthesiologist during this type of surgery is to maintain stable hemodynamics intraoperatively and to provide adequate pain relief post operatively as these surgeries have a large abdominal incision and extensive tissue trauma and viscera manipulation intraoperatively , causing severe pain. If this pain is not treated adequately, it can cause detrimental physiological effects like shallow (low tidal volume) breathing, unable to cough, retention of secretion. These can lead to postoperative respiratory complications like atelectasis, pneumonia, respiratory distress/failure.

In our study we investigated the effect of low dose ketamine infusion on intra-operative hemodynamics during major abdominal surgeries. Ketamine is an NMDA receptor antagonist and provides with both analgesic and antihyperalgesic effect. Ketamine has unique sympathomimetic property by this effect it ketamine help in maintenance of stable hemodynamics intraoperatively.

The anesthetic dose of ketamine (1-2 mg/kg are associated with psychomimetic side effects. But the literature shows that subanesthetic dose of ketamine which is < 1mg/kg/hr have very minimal psychomimetic side effects. So, now the interest have been developed in use of ketamine in subanesthetic low dose because of its potent analgesic effect, antihyperalgesic efffects, opioid sparing effect and neuroprotective effect even in low doses.

In our study, we included 60 patients out of which 30 patients were in Group K and 30 patients were included in Group C, P value >0.05 for Both mean age and mean weight, thus both the groups were comparable for age and weight parameter. There was no significant difference between mean duration of surgery.

Hemodynamic parameters were monitored throughout the surgery. In inter group comparison, mean pulse rate was compared between the two groups and found no significant difference throughout the intraoperative period (P>0.05). In intragroup comparison, mean pulse rate was compared with baseline pulse rate in both the groups. In Group K, there was statistically significant (P<0.05) difference in mean pulse rate (i.e. pulse rate was reduced from baseline value) after 60 minutes of surgery and remained so throughout the surgery (from which at 2 hour, 2 hour 15 mintues, 2 hour 30 minutes,3 hour 30 minutes and at 3 hour 45 minutes, difference was highly significant i.e. P<0.001) while in Group C, there was no significant difference statically in mean pulse rate (P > 0.05) at just after induction, 15 minutes ,2 hour 45 minutes,3 hour 45 minutes, 4 hours 30 minutes, 5 hours, 5 hours 30 minute and just after extubation. In remaning period of time, the difference was statistically significant i.e. pulse rate was reduced from base line (P<0.05). We considered it clinically significant when the difference was beyond the range of 20% from the baseline.The mean pulse rate was significantly reduced at 3 hour 30 minutes and remained so throughout the surgery in Group K and it was not clinically significant while in Group C, mean baseline pulse rate was reduced clinically significantly at 5 hr, 5 hr 15 mins and 5 hr 45 mins. Amr Samir Wahdan et al (2020)[4]and Shruti Jain et al (2022)[6] have observed no significant difference in mean heart rate between the two groups as in our study.

Inter group comparison of Mean Arterial Blood Pressure between the two groups was not significant throughout the study (P>0.05). In intra group comparison with baseline, Group K has statistically significant difference in mean arterial blood pressure from 60 mints to 2 hr 30 mints (P<0.05). The MAP remained within the range of 20 % of baseline, So it was not clinically significant. Thus,

throughout the intraoperative period MAP remained stable while in Group C, mean arterial blood pressure difference at 45 mints,120 mints, 3 hr 15 mints and at 4 hr 15 mints it were highly significant (P<001). MAP reduced significantly and the hypotension is significant clinically also. We found stable hemodynamics in ketamine as compared to the control group.

We found profound hypotension in Group C as patient required 3 doses (18mg) of ephedrine.Thus it was observed that Ketamine helps to maintain stable hemodynamics in such a long duration abdominal surgeries. Amr Samir Wahdan et al (2020)[4], Shruti Jain et al (2022)[6]and S. kaur et al (2015)[7] observed no significant difference in mean Arterial BP at different time period between Group K and Group C. Thus like our study MAP was comparable between both the groups.

In our study; In Group K, 26% of the patients required fentanyl intraoperatively while in Group C 43% of patients required fentanyl and this difference was statistically significant (P>0.05). From this results it was proven that Ketamine have significant opioid sparing effect. Mohammed Hassan et al (2020)[10] and Mitchell T Seman et al (2021)[5] have observed less intraoperative fentanyl consumption, thus, their results are consistent with our results.

There was no significant difference in VAS score in both group at 6 hour and 12 hours interval postoperatively. The difference in mean VAS score was statistically significant upto 3 hours postoperatively (P<0.05), from which at 60 mints it was highly significant (P<0.001, P=0.0004).

DA Aderinto et al (2021)[8] have found no significant difference in median NRS for first 6 hours in contrary to our study. Mitchell T Seman et al (2021)[5] observed overall lower pain scored in ketamine group, but the difference were not statistically significant (P>0.05). Maximum pain score was lower in ketamine group for first 24 hours (5.9 VS 7.8, P=0.0475) as in our study.

Tramadol 100mg was given as rescue analgesic whenever the postoperative VAS score was ≥4 at various time intervals in our study and we found that In Group K, mean of total requirement of tramadol postoperatively in 12 hour was 193.33 ± 90.71 mg while in Group C it was 266.6 ± 84.4 mg (P<0.05, P=0.002). S. Kaur et al (2015)[7] have observed that in Group K 5 patients (12.5%) and in Group C 40 patients (100%) required rescue analgesic IV morphine in dose of 4.6 ± 1.48 mg vs 17 ± 1.7 mg, P=0.001, which was statistically significant. Ranadhir Mitra et al (2017)[9] observed that higher amount of fentanyl (117.9 ± 44.8 mcg) was consumed in placebo group), (P=0.0001, P <0.001) compared to ketamine and dexmedetomidine group.

The limitations of our study includes that as our sample size was small (does not include pediatric population also) and assessment of pain is difficult with VAS scoring system because pain is a subjective feeling, our result may not be generalized.

From this study we concluded that Intraoperative low dose ketamine infusion provides stable intraoperative hemodynamics and perioperative analgesia, with its potent opioid sparing effect and it should be considered as an effective and safe component of multimodal analgesia.

Declaration: Article has not been submitted/ published in any other journal. · Order of Authorship as placed in Manuscript is final and accepted by all.

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