Original Research Article

Comparative evaluation of safety and efficacy of epidural bupivacaine with morphine and ketamine vs epidural bupivacaine with morphine alone for post-operative analgesia

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Abstract

Background: Adding a small-dose of ketamine provides better postoperative analgesia and reduces morphine consumption after major abdominal surgery. Psychomimetic effects are the most troubling side-effects of ketamine. Hence evaluation of the safety and efficacy of adding ketamine to epidural bupivacaine with morphine is the need of the hour.

Materials and methods: The study was a randomized controlled trial conducted in the Department of Anesthesia, Department of Anesthesiology, Government Mohan Kumaramangalam Medical College and Hospital between April 2015 to March 2016. Study on 60 subjects of ASA I and II category randomized into two groups undergoing elective abdominal surgeries was done. 30 subjects in the study group received ketamine 0.2 mg/kg in addition to epidural morphine 0.05 mg/kg with 0.125% bupivacaine alone received in the control group for post-operative analgesia. The subjects were monitored for 24 hours.

Results: The mean time for onset of analgesia and median duration of analgesia was 6.10 ± 1.27 minutes, 13.73 ± 3.10 hours respectively in ketamine group (Group I) whereas it was 12.53 ± 2.08 minutes, 8.27 ± 1.08 hours respectively in the control group. There was no complication or ketamine related side effects in the ketamine group compared to one in the control group.

Conclusions: A multimodal combination comprising of low-dose epidural ketamine with morphine not only results in effective postoperative analgesia but also decreases the rescue analgesia requirement, without any increase in side-effects.

Key words

Ketamine, Morphine, Bupivacaine, Post-operative pain, Epidural analgesia.

Introduction

Epidural analgesia refers to local anesthetics and adjuvants injected into the epidural space. It plays a significant role in the alleviation of postoperative pain [1]. In the past few decades, it has evolved as one of the major elements of the multimodal approach in accomplishing the goal of adequate and effective control of post-operative pain besides offering superior results on comparison with systemic opioids. It also reduces the unfavorable physiology experienced during the surgery. The presence of opioid receptors in spinal cord allows the use of morphine epidurally or intrathecally for managing pain [2]. The addition of low-concentration bupivacaine in epidural morphine provides better analgesia than morphine only and has less opioid-related side effects [3]. Ketamine is a *N*-methyl-D-aspartate receptor antagonist. Ketamine eliminates afferent noxious stimulation peripherally, hence also preventing the central sensitization of nociceptors thereby leading to the potentiation of morphine analgesia [4, 5]. It has been demonstrated that a regimen of small-dose ketamine and morphine prevented severe postoperative pain which was not relieved previously by morphine alone [5]. Ketamine also reduced morphine consumption besides giving subjective feelings of well-being, without unacceptable side effects. Sethi M, et al. (2012) [6] also observed that adding small-dose ketamine provides better postoperative analgesia and reduces morphine consumption after upper abdominal surgery. Wong CS, et al. (1996) [7] also observed the same in major knee surgeries. But it is not being commonly used due to the side effects of ketamine such as hallucination or delirium. So we conducted a randomized controlled trial in subjects undergoing major abdominal surgeries with the objective of evaluating the safety and efficacy of adding ketamine to epidural bupivacaine with morphine for post-operative analgesia.

Objectives

- To evaluate the safety and efficacy of epidural bupivacaine with morphine and ketamine vs epidural bupivacaine with morphine alone for post-operative analgesia after major abdominal surgeries

Materials and methods

The study was a randomized controlled trial conducted in the department of Anesthesia, Department of Anesthesiology, Government Mohan Kumaramangalam Medical College and Hospital between April 2015 to March 2016. The study had included 60 subjects randomly allocated to one of the following intervention groups.

Group I: 0.125% bupivacaine with morphine 0.05 to 0.1 mg/kg with maximum dose of 5mg and ketamine 0.2-0.5 mg/kg with maximum dose of 1 mg/kg.
Group II: 0.25% bupivacaine with morphine 0.05 to 1 mg/kg with maximum dose of 5 mg.

Randomization was done using computer generated random number sequence. Allocation concealment was done using serially numbered opaque envelops. Participant blinding was done, but investigator blinding was not possible considering the nature of intervention. Statistician analyzing the data was blinded for the intervention. The study was approved by institutional human ethics committee and informed written consent was obtained from all the participants.

Inclusion criteria

- Age: 18-65 years.
- ASA: 1 and 11.
- Surgery: Elective abdominal surgery.
- Who have given valid informed consent

Exclusion criteria

- Not satisfying inclusion criteria.
- Patient posted for emergency surgery.
- Contraindication for regional blockade.
- Known sensitivity to the drugs.
- Pregnant females.
- History of opoid addiction.
- History of psychological disorder.
- ASA>2.

Pre-operative assessment and recording of vitals

The age, weight, height and vital parameters like pulse rate, blood pressure and baseline investigations like hemoglobin, blood sugar, urea, creatinine, chest X-ray, ECG were checked. Thorough examination of all the systems and airway assessment were done.

Methods

The base line blood pleasure, heart rate and oxygen saturation were recorded. Under strict aseptic precautions, prior to introduction of anesthesia epidural catheter was placed in T8-T10 intervertebral space using Tuohy's, needle with loss of resistance technique and the test done of 3ml of 1.5% lignocaine was given through the epidural catheter. In both the groups anesthesia was induced with thiopentone 5 mg/kg and fentanyl 2 mic/kg, intubated with atracurium 0.5 mg/kg and anesthesia was maintained with atracurium 0.1 mg/kg and Volatile Nitrous Oxygen mixture. Intra operative analgesia was maintained with intermittent doses of fentanyl. After end of procedure reversal of residual neuromuscular blockade with neostigmine 50 mic/kg and glycopyrrolate 10 mic/kg, then the patient was shifted to PACU. (post-anesthesia care unit)

Monitoring in the Post Anesthetic Care Unit (PACU)

In the PACU the patient was assessed for pain intensity using the 10-point vas score. Visual analogue scale (VAS) was explained to patients. The patients were shown a 10-cm scale marked 0-10cm on a block paper and told them 0 represented WORST POSSIBLE PAIN.

VAS score

0-DOES NOT HURT
2-HURTS JUST A LITTLE BIT
4-HURTS A LITTLE MORE
6-HURTS EVEN MORE
8-HURTS A LOT
10-HURTS AS MUCH AS U CAN IMAGINE

If the VAS score was more than 2 epidurals was activated. The total volume was 12-14 ml in the both the groups.

Group-1: 0.125% bupivacaine with morphine 0.05-0.1 mg/kg with max dose of 1 mg/kg.
Group-2: 0.25% bupivacaine with morphine 0.05-1mg/kg with maximum dose of 5mg. In the groups the following parameters recorded.

1. Onset of analgesia
2. Duration of analgesia
3. VAS score
4. Sedation score

Monitoring of vitals

Heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressures at 0 min,15 min, 30 min,1 hour, 2 hour, 4 hour, 6 hour, 8 hour, 12 hour, 16 hour, 20 and 24 hour intervals. Rescue analgesic requirements were recorded for 24 hours.

Recording of adverse events

The adverse effects like pruritus, respiratory, depression, nausea, vomiting, hallucinations and delirium were recorded.

Primary outcome measures

- Onset of analgesia
- Duration of analgesia
- Pain at rest and movement at 0.15 min, 30 min, 1, 2, 4, 6, 8, 12, 16, 20, 24 hours.

- VAS score, sedation score. (Ramsay sedation score)
  1. Patient anxious, agitated and ressless.
  2. Cooperative, oriented and tranquil.
  3. Responds to commands.
  4. Exhibits brisk response to light, glabellar tap or loud auditory stimulus.
  5. Exhibits slugglish response to light, glabellar tap or loud auditory stimulus
  6. Exhibit no response.
- Rescues analgesic requirement

Secondary outcome measures

- Heart rate
- Systolic blood pressure
- Diastolic blood pressure
- Mean arterial pressure

In both the groups the onset of analgesia, the duration of analgesia using VAS score, systolic, diastolic and mean blood pressure, heart rate, rescue analgesic requirements, incidence of complications was recorded for 24 hours.

One or two patients had vomiting, were managed with Inj. Ondansetron 8 mg intravenously. One or two patients had hypotension, fall in systolic blood pressure more than 30% from base line were managed with iv fluids and incremental doses of Inj. ephedrine 6 mg iv. None of the patients experienced hallucinations or delirium.

All the quantitative parametrs were compared between two groups using independent sample t-test after checking fro normal distribution. All the qualitative variables were compared using chi square test/ Fisher's exact test. The time changing variables were compared using mixed method repeated measures ANOVA. IBM SPSS statistical software version 21 was used for analysis.

Results

A total 60 people were included in the analysis

The mean age of group I was 46.33 ± 10.20 and group II was 41.70 ± 10.81, the association between two groups was statistically not significant (P value 0.09). Among the 30 people with group I, 14 (46%) were male and remaining 16 were female. Among the 30 people with group II, 14 (46.67%) were male and remaining 16 (53.33%) were female. The difference in the proportion of gender between groups was statistically not significant (P value 1.000). The mean weight (in kg) of group I was 57.23 ± 3.93 and group II was 58.60 ± 6.49, the association between two groups was statistically not significant (P value 0.33). Among the 30 people with group I, 14 (46.67%) were ASA status I and remaining 16 (53.33%) were ASA status II. Among the 30 people with group II, 24 (80%) were ASA status I and remaining 6 (20%) were ASA status II. The difference in the proportion of ASA status between groups was statistically significant (P value 0.007) as per **Table - 1**.

The mean time taken for onset analgesia in group I was 6.10 ± 1.27 minutes and group II was 12.53 ± 2.08 minutes, the association between two groups was statistically significant (P value <0.001). The mean analgesia duration in group I was 13.73 ± 3.10 hours and group II was 8.27 ± 1.08 hours, the difference between two groups was statistically significant (P value <0.001) as per **Table - 2**.

The median VAS score was consistently lower in group 1 as compared to group 2 throughout the post-operative period (**Figure - 1**).

The heart rate was comparable between the two study groups throughout the post-operative period, with no statistically significant difference (**Figure - 2**).

The heart rate was comparable between the two study groups throughout the post-operative period, with no statistically significant difference (**Figure - 3**).

The heart rate was comparable between the two study groups throughout the post-operative period, with no statistically significant difference (**Figure - 4**). Trend line comparison of mean arterial pressure between two groups was as per **Figure – 5**.

Table - 1: Comparison of Baseline parameters between two study groups (N=60).

Parameter	Group		P value
	Group I (N=30)	Group II (N=30)	
Age (Mean± STD)	46.33 ± 10.20	41.70 ± 10.81	0.09
Gender			
Male	14 (46.67%)	14 (46.67%)	1.000
Female	16(53.33%)	16(53.33%)	
Weight (in Kg) (Mean± STD)	57.23 ± 3.93	58.60 ± 6.49	0.33
ASA status			
I	14 (46.67%)	24(80%)	0.007
II	16(53.33%)	6(20%)	

Table - 2: Comparison of onset and duration of analgesia between two study groups (N=60).

Group	Mean± STD	Range	P value
Onset analgesia drug (in minutes)			
Group I	6.10 ± 1.27	5-10	<0.001
Group II	12.53 ± 2.08	9-15	
Analgesia drug duration (in hours)			
Group I	13.73 ± 3.10	6-18	<0.001
Group II	8.27 ± 1.08	6-10	

Figure - 1: Trend line comparison of mean visual analog scale between two groups (N=60).

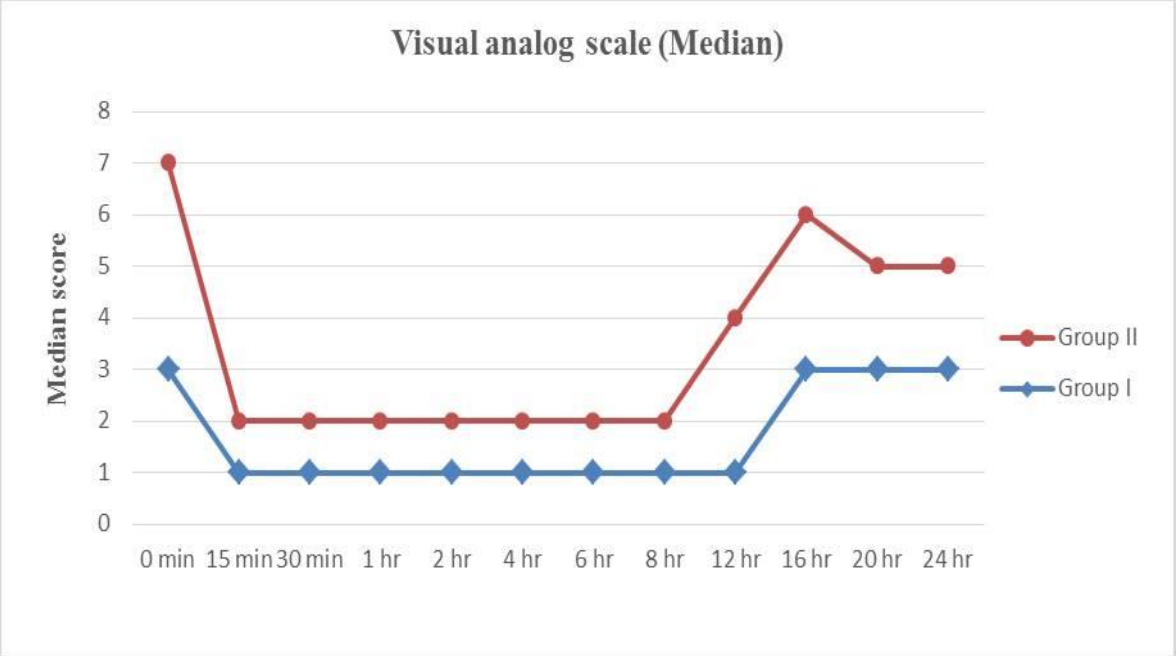

Table - 3: Comparison of incidence of complication between two groups (N=60).

Incidence of complication	Group	
	Group I (N=30)	Group II (N=30)
No complication	29 (96.67%)	30 (100%)
Pruritis	1 (3.33%)	0 (0%)

**No statistical test was applied- due to 0 subjects in the cells.*

Figure - 2: Trend line comparison of mean heart rate between two groups (N=60).

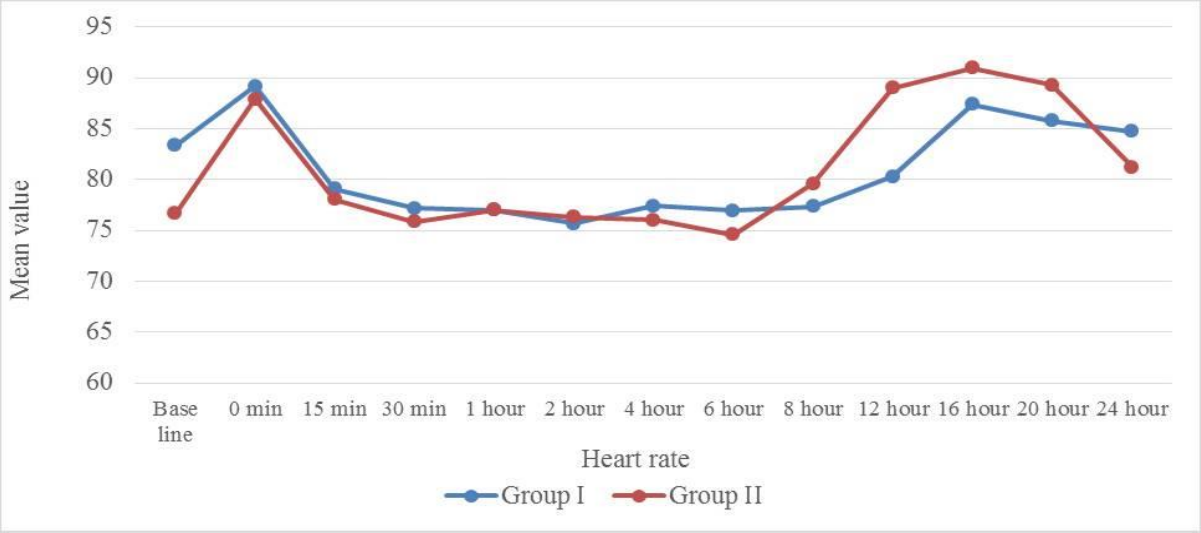

Figure - 3: Trend line comparison of mean systolic blood pressure between two groups (N=60).

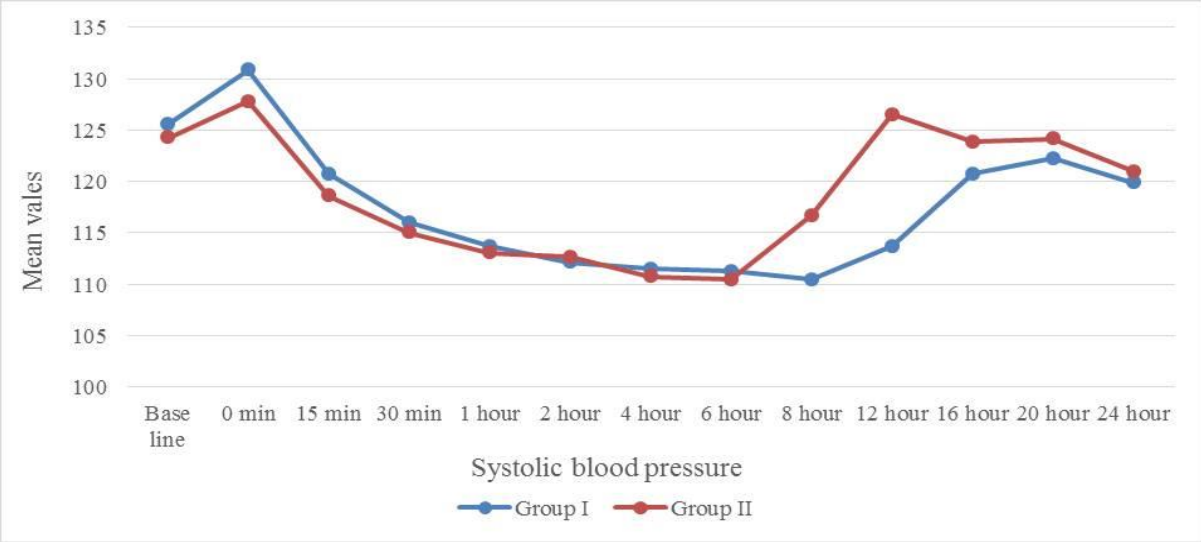

Figure - 4: Trend line comparison of mean diastolic blood pressure between two groups (N=60).

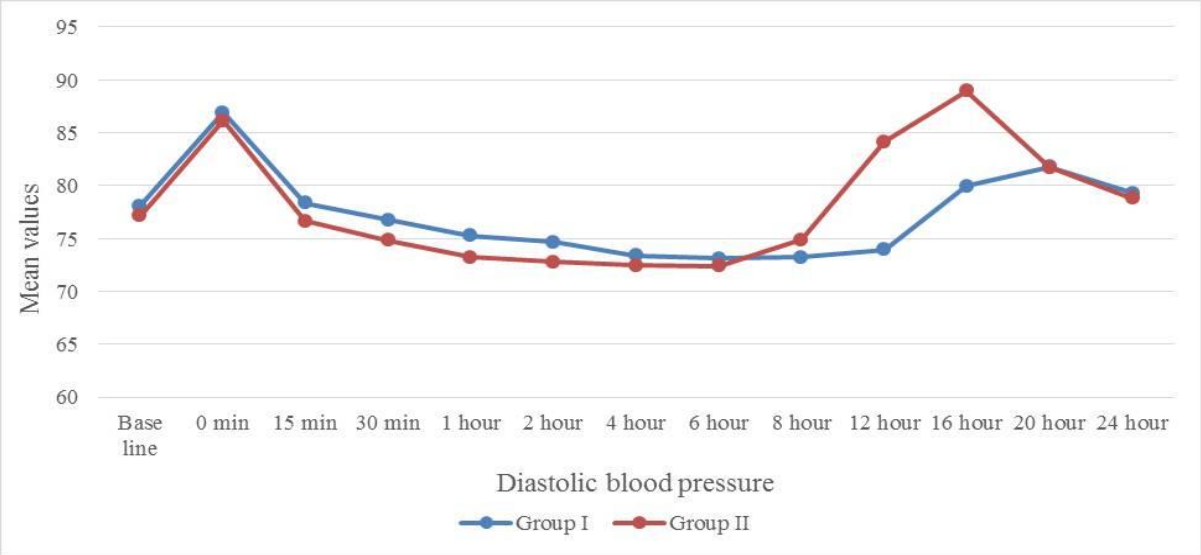

Figure - 5: Trend line comparison of mean arterial pressure between two groups (N=60).

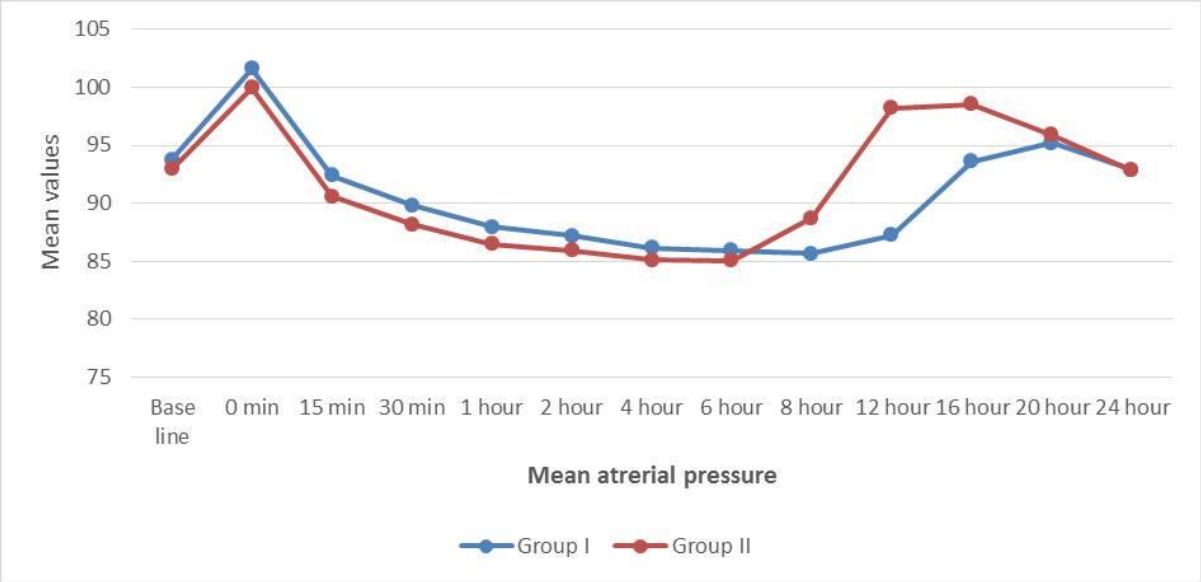

Table - 4: Comparison of rescue analgesic requirements (in time) between study groups (N=60).

Rescue analgesic requirements (in time)	Group				P value
	Group I (N=30)		Group II (N=30)		
	Not required	Required	Not required	Required	
2 hour	30(100%)	0	30(100%)	0	-
4 hour	30(100%)	0	30(100%)	0	-
6 hour	29(97%)	1(4%)	21(70%)	9(30%)	0.05
8 hour	26(87%)	4(13%)	0	30(100%)	**
12 hour	10(34%)	20(67%)	1(4%)	29(97%)	0.003
16 hour	2(7%)	28(94%)	1(4%)	29(97%t)	0.55
20 hour	4(13%)	26(87%)	2(7%)	28(94%0	0.39
24 hour	21(70%)	09(30%)	14(47%)	16(54%)	0.07

In group I, 1 (3.33%) only one participants had PRU incidence of complication (**Table – 3**).

Higher proportion of the subjects in group II had required rescue analgesic from 6th hour to 24 hours (**Table – 4**).

Discussion

Epidural analgesia is most commonly provided using a combination of local anesthetic and an opioid. Morphine is commonly used for providing postoperative epidural analgesia. On comparison with either of them alone [8], their combination provides superior postoperative analgesia with lower dose of local anesthesia and less opioid-related side-effects. Stimulation of NMDA receptors by morphine, especially in larger doses may reduce and shorten its anti-nociceptive effect [4, 9]. Combining NMDA-receptor antagonists with both opioid and non-opioid analgesics may increase their analgesic potency [10]. NMDA receptor antagonists inhibit hyperalgesia caused by inflammation, tissue and nerve injury [11]. The primary aim of our study was to evaluate the effect of adding low dose epidural ketamine with bupivacaine and morphine for post-operative analgesia after major abdominal surgeries.

In our study, we randomized the subject into two groups of 30 each – The ketamine group and the control group. Both the groups had a similar anthropometric profile. They were comparable in terms of age, sex and weight. The difference

between the groups was not statistically significant. In a similar study by Sethi M, et al. (2011) [6], the mean age of subjects was 5 to 10 years higher than our study subjects. Most of the study participants in our study were in the age group of 41 to 50 years. The difference in proportion of subjects in each group with respect to ASA category was not statistically significant in our study. Our primary outcome variables were mean time for onset and mean duration of analgesia.

In our study, mean time for onset of anesthesia was 6.43 minutes lower in the ketamine group compared to the control group. The mean time for onset of analgesia was 6.10 ± 1.27 minutes in ketamine group (Group I) in our study whereas it was 12.53 ± 2.08 minutes in the control group. This difference of 6.43 minutes lesser time to onset of analgesia in ketamine group was statistically very significant with a p value of 0.001. Similarly Subramaniam K, et al. (2001) [12] observed that onset of analgesia was faster ($p < 0.001$) in Ketamine Group 2 (11 min) than in control Group (25 min) when they used analgesics for postoperative pain relief following major upper abdominal surgery.

Analgesia lasted longer in ketamine group with reduced need for rescue analgesia compared to the control group in our study similar to that observed by several authors [6, 7, 12-14].

In our study, the median duration of analgesia was 13.73 ± 3.10 hours in ketamine group (Group I) whereas it was only 8.27 ± 1.08 hours in the control group. This difference was statistically very significant with a p value of 0.001.

Similarly Subramaniam K, et al. (2001) [12] observed that the median duration of analgesia was significantly ($p < 0.01$) longer (19.8 +/- 9.8 hours) in Ketamine Group compared to control Group (12.8 +/- 6.2 hours) by evaluating the efficacy of combining epidural ketamine with morphine for post-operative analgesia compared to morphine alone. In our study, the need for rescue analgesia was significantly very less in Ketamine group compared to control group at 6 hours ($p=0.05$), 8 hours ($p=0.001$) and 12 hours ($p=0.003$) of follow up.

Similar to our observations, Sethi M, et al. (2011) [6] observed that mean morphine consumption in group I after 1st postoperative day was 8.38±2.85 mg in control group compared to 6.81±1.35 mg ($P<0.05$) in ketamine group. They used a continuous infusion of 0.0625% bupivacaine, morphine sulphate (preservative free) 0.05 mg/ml and ketamine hydrochloride (preservative free) 0.2 mg/ml for one group and 0.0625% bupivacaine and morphine sulphate (preservative free) 0.05 mg/ml for another group. Post-operative analgesia was done with Patient Control Epidural Analgesia (PCEA). In our study, they received ketamine 0.2 mg/kg in addition to epidural morphine 0.05 mg/kg with 0.125% bupivacaine alone received in the control group for post-operative analgesia.

Similarly Subramaniam K, et al. (2001) [12] observed that total number of supplemental doses of epidural morphine required in the first 48 hours postoperatively was also significantly less ($p < 0.005$) in ketamine Group compared to control Group.

Wong CS, et al. (1996) [7] from the results of their study also observed that Ketamine, although not itself an epidural analgesic agent, potentiates the analgesic effect of morphine, especially when administered as a pretreatment and they also observed that ketamine alone produced no significant pain relief.

With regards to the subjective analgesia scoring, although the Median VAS scores were higher at the end of 20 and 24 hours follow up in Ketamine group in our study, the median VAS score was 1 in ketamine group (Group I) up to mean duration of 13.73 hours and 1 in control group (Group II) up to 8.27 hours which was comparable between the groups.

Similar to our study Sethi M, et al. (2011) [6] observed that pain relief at rest and at movement after 6, 12, 24 and 48 hours, postoperatively was significantly better in ketamine group ($P<0.05$) than in control group. Similar results were also observed by Chia YY, et al. (1998) [15] and Wu CT, et al. (2000) [14].

The Hemodynamic variables such as Heart rate, Systolic, Diastolic and Mean blood pressure were also comparable between the groups. The mean differences was not statistically significant except at 12 hours of follow up for Heart rate, Mean arterial pressure and systolic B.P and at 8,12 hours for Diastolic B.P. The higher rate and this difference could be due to the fact that median duration of analgesia was 13.73 hours in ketamine group (Group I) whereas it was only 8.27 hours in the control group. Hence between 8 to 12 hours of monitoring during follow up, this difference in hemodynamic variables could be noted. Our hemodynamic study findings were almost similar to that observed by Wong CS, et al. (1996) [7] and Chia YY, et al. (1998) [15].

In our study, there was no ketamine associated side effects in the study group. Also there was no incidence of morphine induced side effects in ketamine group compared to one in the control group. No serious adverse effect, such as respiratory depression or hemodynamic instability was noted in either of the groups. Psychomimetic effects such as hallucination or delirium, the most troubling side-effects of ketamine, was also not observed in any of our study subjects. Wong CS et al(1996)[7] also similarly observed that the resulting lowered dosage of epidural morphine needed for postoperative pain relief in turn, decreases the incidence of side effects. Also there was no increase in side effects due to ketamine. Weinbroum AA, et al. (2003) [5], Subramaniam K, et al. (2001) [12] also observed a similar side effect profile in their study advocating the safety in adding ketamine to morphine.

Opioid-induced hyperalgesia [4] is a phenomenon where there is a lowering of pain threshold, with opioid administration manifesting as apparent opioid tolerance, worsening pain notwithstanding increasing opioid doses, with abnormal pain symptoms. This phenomenon is a challenge faced by anesthesiologists in perioperative care, which could be overcome by adding ketamine.

A multimodal combination comprising of low-dose epidural ketamine with morphine not only results in effective postoperative analgesia but also decreases the rescue analgesia requirement, resulting in decreased morphine-related side-effects.

Conclusion

The addition of low dose ketamine (0.2 mg/kg) epidurally with bupivacaine and morphine accelerates the onset of analgesia and also increases the mean duration of analgesia, without an increase in incidence of side effect on comparison with epidural bupivacaine and morphine alone thereby resulting in effective post-operative analgesia in subjects undergoing major abdominal surgeries. The required doses of rescue analgesia was also lesser in the study group compared to the control group.

Limitations

In our study, the subjects were followed up only for 24 hours due to practical feasibility. We could not investigate the effect of ketamine alone without morphine in post-operative analgesia and confounding effect of morphine and bupivacaine which could affect our study results.

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