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COMPARISON OF KETAMINE AND MAGNESIUM AS ADJUVANT TO BUPIVACAINE IN EPIDURAL ANAESTHESIA FOR ABDOMINAL SURGERY.

Anaesthesiology

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ABSTRACT

BACKGROUND: Neuraxial blocks provide anaesthesia along with post operative pain relief. Various adjuvants have been added to local anaesthetic drugs in epidural anaesthesia to improve outcome and reduce side effects related to toxicity of local anaesthetics .The aim of the study is to compare the effects of magnesium sulphate versus preservative-free ketamine as an adjuvant to epidural bupivacaine in abdominal surgeries.

MATERIALS AND METHODS: After obtaining informed consent, the patients were divided into 3 groups of 30 each ,Group I: bupivacaine 0.5% (19 ml) + saline 0.9% (1 ml), Group II: bupivacaine 0.5% (19 ml) + ketamine 50 mg (1 ml).,Group III: bupivacaine 0.5% (19 ml) + magnesium sulphate 75 mg (1 ml).

RESULTS.

Time taken to T6 block, the time from the epidural to surgical incision and time for two segment regression was significantly lower in group II as compared to groups I and III with a p value of 0 .001,0.001,0.006 respectively. Time of first epidural top up was significantly higher in group II than group I and III with p-value=0.003. . VAS(mean) was lowest in the group II and highest in the group I whereas VAS of group III was in between these two values, being statistically significant at 90 min with a p-value of 0.01. The hypotension was found in 83.3% of Group I, 26.7% in Group II and 60% in Group III and the difference was statistically significant (p=0.001).

CONCLUSION

Our findings establish ketamine as a predictable and safe adjuvant to epidural bupivacaine for rapid and prolonged anaethesia with stable hemodynamic profile, better perioperative VAS scores, satisfactory surgical conditions and fewer side effects.

KEYWORDS

Epidural, Magnesium sulphate, preservative free ketamine, bupivacaine, postoperative analgesia, abdominal surgeries.

INTRODUCTION

Epidural anaesthesia is a safe technique with the advantage of providing surgical anaesthesia and prolonged postoperative pain relief and benefits like improved respiratory functions, decreased perioperative cardiac complications, earlier mobilization and less chances of DVT with shorter hospital stay. It can be used as a sole anesthetic agent for lower abdominal surgeries and as an effective treatment of operative pain as it blunts autonomic, somatic and endocrine responses. The advantage of epidural over spinal anaesthesia is the ability to maintain continuous anaesthesia after placement of an epidural catheter, thus making it suitable for procedures of long duration and also enabling the use of this technique into the postoperative period for analgesia, using lower concentrations of local anaesthetic drugs or in combination with different agents.

0n the other hand, the main disadvantages are a slow onset, a density of block not comparable to that of spinal anesthesia, migration of epidural catheter into intravenous or sub arachnoid space and side effects due to sympathetic blockade: for eg; hypotension in approx 30-40% of the cases, bradycardia approx 13%, nausea approx 18%, vomiting approx 7%, dysarrrhythmia approx 2%,[1] and, occasionally, need for introducing general anesthesia.

Adjuvants (such as opioids, clonidine, neostigmine, epinephrine, ketamine, magnesium) have been added to local anaesthetic drugs to improve analgesia, reduce morbidity and to reduce local anaesthetic doses and side effects.

Magnesium is the fourth most plentiful cation in our body[2] .It has antinociceptive effects in animal and human models of pain. James 1992[3], Lysakowsky et al 2007[4] in a systematic review mentioned that it may be worthwhile to further study the role of supplemental magnesium in providing perioperative analgesia because this is a relatively harmless molecule, cheaper and potential antinociceptive effect.

Bupivacaine is a long acting local anesthetic belonging to amino amide group. Epidural Bupivacaine with ketamine can produce surgical anesthesia and decrease the incidence of hypotension or respiratory depression.

Ketamine is a noncompetitive antagonist of NMDA receptors[5]. It is due to blockade of central and peripheral NMDA receptors and an antinociceptive action complementary to that of the other drugs used. Ketamine reduces the temporal summation (wind up) of pain that underlies the induction of central sensitization [6] and thus prevents central and peripheral sensitization[7].Based on data from epidural and caudal use, ketamine gains rapid access to the systemic circulation with high bioavailability. However the resorption and uptake of peripheral or neuraxial ketamine has not yet been systematically analyzed. Further no clinical studies have examined the effect of magnesium sulphate versus ketamine administered epidurally as an adjuvant to epidural bupivacaine. We, therefore, conducted a prospective, randomized, double blind study to compare the effects of ketamine versus magnesium sulphate co administered epidurally as adjuvant to bupivacaine for abdominal surgeries.

AIMS AND ABJECTIVE

The primary aims and objectives of this study were to establish the effects of adding magnesium sulphate and ketamine as adjuvants to epidural bupivacaine on onset of anesthesia, duration of analgesia, any adverse effects, haemodynamic responses and complications. Secondary aim is to establish the advantages of epidural anaesthesia as a sole anesthetic for lower abdominal surgeries with addition of ketamine and magnesium as adjuvant.

MATERIALS AND METHODS

After obtaining approval from the ethical committee and taking informed consent from all patients, this prospective, randomized, double blind study was conducted in King George's Medical University over a period of July 2017-August 2018 on ninety(ASA) I or II patients, 18-60 years of age, undergoing abdominal surgery .Patient having any contraindication for epidural anaesthesia and any systemic disease like diabetes mellitus, hypertension, respiratory disorders, renal, cardiac or hepatic dysfunction, were excluded from our study.A pre-anaesthetic checkup was done and past medical records were reviewed. Patients were familiarized with the Verbal Rating Score (VRS) (0: no pain, 100: worst pain) a day before surgery. Premedication with 0.25 mg alprazolam orally night before surgery was prescribed.

After the patients were taken in the operation theater standard non-invasive monitors like electrocardiogram, noninvasive blood pressure and pulse oxymeter were applied and baseline pulse rate (P.R), blood pressure (systolic, diastolic, and mean), and oxygen saturation (SpO2) were noted. An intravenous access was established using 18-gauge intravenous cannula. All the patients were preloaded with lactated Ringer's solution (10 mL/kg body weight).

Under strict aseptic precautions, all patients were given epidural with the 18 G Tuohy needle at L 3-4 using a loss of resistance technique and a 20 G epidural catheter was then advanced for 3 to 5 cm into the epidural space. Correct placement of epidural catheter was verified with a test dose of 3 ml epidural lignocaine 2% with adrenaline (1: 2, 00,000).

The patients were divided randomly into following three groups according to the epidural medications used:

Group I: bupivacaine 0.5% (19 ml) + saline 0.9% (1 ml).
Group II: bupivacaine 0.5% (19 ml) + ketamine 50 mg (1 ml).
Group III: bupivacaine 0.5% (19 ml) + magnesium sulphate 75 mg (1 ml)

Sensory block was assessed bilaterally by pin prick with a short hypodermic needle in the midclavicular line. Motor blockade was assessed by using modified Bromage scale (0: no motor block; 1: inability to raise extended legs; 2: inability to flex knees; 3: inability to flex ankle joints[8].

Per-operative monitoring of heart rate, noninvasive arterial blood pressure and SpO2 measurements was done in three groups preoperatively, intraoperatively and during shifting. Hypotension was defined as systolic blood pressure <90 mmHg or less than 20% of baseline. In cases of episodes of hypotension and bradycardia, boluses of 6mg of mephentermine and 0.5mg atropine was given intravenously.

Sedation assessment was assessed on a four point scale (Grade 0, awake and alert; 1, mildly sedated, easily aroused; 2, moderately sedated, aroused by shaking; 3, deeply sedated, difficult to be aroused by physical stimulation)[9].

After preoperatively explaining the patients, they were asked to evaluate their pain on the standard 100 point visual analogue pain scale (VAS 0 = no pain, VAS 100 = worst possible pain).

At any period of time, when the VAS score was found to be >40, it was considered as failure of epidural block and was converted to general anaesthesia. These patients were then excluded from our study.

Time to two segment regression from first epidural drug loading was taken as a cut off for the next top up irrespective of the VAS scores. In the event of regression a top up was given with bupivacaine 0.25% (8 ml) by the anesthesiologist inside the operation theatre.

Occurrence of adverse effects if any, were recorded. All the data were collected and statistical analysis was done by ANOVA using the computer software statistical package for social sciences(SPSS) followed by post hoc comparison tests

Statistical analysis

The results are presented in mean±SD and percentages. The Chi-square test was used to compare the gender differences between the groups. The one way analysis of variance was used to compare the study parameters among the groups followed by Tukey's post hoc comparison test. The p-value<0.05 was considered significant. All the analysis was carried out by using SPSS 16.0 version.

RESULTS

Demographic Variables:

The demographic variables namely mean age of the patients, height, weight and BMI were comparable in all three groups and had no impact on the result of our study.

[Table 1]

Table-1: Demographic variables of the patients among the groups

	Group I (n=30)	Group II (n=30)	Group III (n=30)	p-value1
Age in years	38.17±8.15	42.73±10.07	42.17±11.08	0.15
Gender				
Male	12 (40.0%)	13 (43.3%)	13 (43.3%)	0.95
Female	18 (60.0%)	17 (56.7%)	17 (56.7%)	
Height in cms	164.66±5.14	162.36±6.87	161.03±7.99	0.11
Weight in kg	62.06±8.46	60.46±59.56	59.56±6.50	0.50
BMI	22.79±2.15	22.82±2.36	22.95±1.70	0.95

Effect on Hemodynamic Variables:

Baseline parameters: The base line heart rates, systolic blood pressure, diastolic blood pressure and SPO2 were similar in all three groups with no statistically significant difference.

The pulse rate was similar (p>0.05) among the groups at pre-op. There was significant (p<0.01) difference among the groups at 5 min to 25 min being lowest in Group II at all the time intervals. The pulse rate became similar (p>0.05) at 30 min to 60 min among the groups and again became significantly different at 90 min till shifting among the groups. [Fig1]

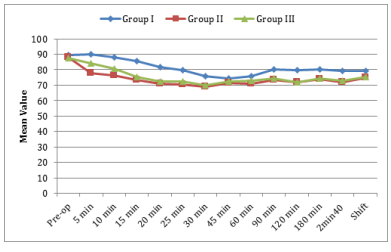

Fig.1: Comparison of pulse rate among the groups

The heart rate in group using Ketamine as adjuvant was lowest, those who received epidural magnesium was intermediate, while heart rate in group using plain bupivacaine was highest at most of time during study.

The SBP was similar (p>0.05) among the groups at pre-op indicating the comparability of the groups in terms of SBP. There was significant (p<0.05) difference in SBP among the groups at all the time intervals being higher in Group II. [Fig 2]

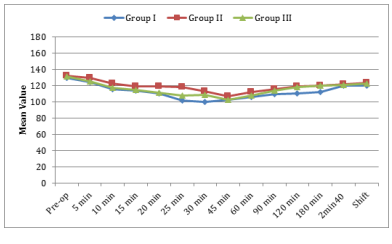

Fig.2: Comparison of SBP among the groups

The DBP was similar (p>0.05) among the groups at pre-op indicating the comparability of the groups in terms of DBP. There was significant (p<0.05) difference in DBP among the groups at all the time intervals being lower in Group III except at 20,45 and 60 minutes. [figure 3]

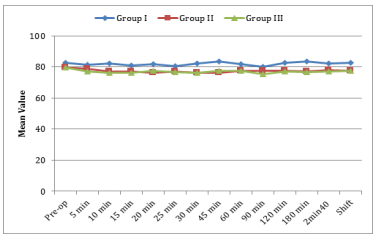

Fig.3: Comparison of DBP among the groups

The VAS was nil among all the groups till 20 minutes, significantly lower at 90 min in Group II compared with Group I and Group III. There was no significant (p>0.05) difference in VAS at other time intervals among the groups.[figure 4]

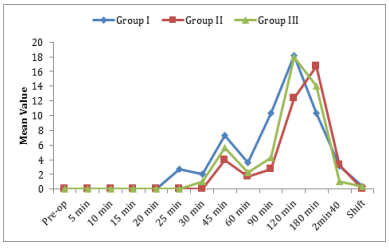

Fig.4: Comparison of VAS among the groups

Time taken to T6 block was significantly (p=0.0001) lower among the groups. The post-hoc pair-wise comparison tests revealed that the time taken to T6 block was significantly (p=0.001) lower in Group II than Group I and Group III. [Table 2] The time from epidural to surgical incision was significantly (p=0.0001) lower among the groups. The post-hoc pair-wise comparison tests revealed that the time from epidural to surgical incision was significantly (p=0.001) lower in Group II than Group I and Group III. (Table2)

Table 2 Comparison of time (in minutes)taken to T6 block,epidural to surgical incision,1st epidural top up and various complications among groups.

	Group 1	Group 2	Group 3	p-value
Time taken to T6 block ±SD (in minutes)	21.03±2.56	11.93±3.11	17.10±3.04	0.0001
Time from Epidural to surgical incision ±SD (in minutes)	26.83±1.93	15.90±2.28	22.70±2.36	0.0001
Time 1st epidural top up ±SD (in minutes)	131.00±32.20	158.33±29.22	144.50±27.67	0.003
Time for 2 segment regression ±SD (in minutes)	119.17±31.73	143.67±28.58	131.17±26.11	0.006
Complications(%)				
Hypotension	83.3	26.7	60	0.001
Bradycardiya	23.3	6.7	13.3	0.001
Shivering	23.3	0.0	0.0	NA

The time of 1st epidural top up was significantly (p=0.0001) different among the groups. The post-hoc pair-wise comparison tests revealed that the time of 1st epidural top up was significantly (p=0.001) higher in Group II than Group I and Group III. (Table2). The ANOVA revealed that the time for 2 segment regression was significantly (p=0.006) different among the groups. The post-hoc pair-wise comparison tests revealed that the time for 2 segment regression was significantly (p=0.001) higher in Group II than Group I and Group III. (Table2)

The hypotension was found in 83.3% of Group I, 26.7% in Group II and 60% in Group III and the difference was statistically significant (p=0.001). However, bradycardia was in 23.3% of Group I, 6.7% in Group II and 13.3% in Group III. Shivering was found only in Group I which was 23.3% (Table2)

Epidural anesthesia using a epidural catheter is good and effective technique for providing anesthesia and analgesia in lower abdominal, pelvic and lower limb surgeries. It enables anesthesiologist to provide prolonged anaesthesia during intraoperative and post-operative periods. Local anesthetics are the most powerful weapon in the armamentarium of epidural anesthesiologist. However, they are associated with major hemodynamic changes when used in epidural anaesthesia. To reduce their side effect many adjuvant have been studied and used so that the concentration and amount of local anaesthetic can be reduced.

DISCUSSION :

The present study was under taken in a tertiary care hospital involving patient of ASA I or II and between 18 to 60 years of age under going elective abdominal surgeries under epidural anaesthesia. We formulated a hypothesis based on previous studies and available literature that Ketamine, being a potent NMDA receptor antagonist [5]is known to provide analgesia and Magnesium possesses antinoceptive effect in animal and human model of pain[3],[4].These drugs reduced the local anaesthetic requirement, improved the quality of block and decreased major hemodynamics swings when used as a adjuvant in epidural anaesthesia. Therefore we used them to compare and analyze their effectiveness and adverse effect in epidural anaesthesia.

The heart rate in group using Ketamine as adjuvant was lowest and the group using saline was highest and the group using magnesium as an adjuvant showed values intermediate between the other two groups. This variation among groups regarding heart rate might be because of better sensory blockade with better analgesic effect in groups with adjuvants as compared to plain bupivacaine. . The mean systolic blood pressure was highest in the group II where used ketamine as adjuvant while systolic blood pressure was lowest in the group I where used plain bupivacaine at most of time during study period except at time of shifting when systolic blood pressure were similar in all three groups with no statistically significant difference. Regarding diastolic blood pressure, statistically significant intergroup differences were seen at all time intervals starting from 5 minutes up to shifting the patient. Therefore we concluded that ketamine provided most stable hemodynamics probably due to reduced stress level by epidural ketamine. In consonance with our findings Slobodan Mihaljevi (2012) [9] and Togal T et al (2004) [10] concluded that adding S-(+)-ketamine to epidurally administered bupivacaine caused no statistically significant changes in arterial blood pressure, heart rate and mean arterial pressure as compared to epidurally administered bupivacaine alone and also found that the vasoactive stress hormone (adrenaline, noradrenaline and cortisol) concentration in plasma decreased after administration of low doses of S-(+)-ketamine epidurally. Regarding duration and onset of anaesthesia Zand et al (2004)[11] conducted a study and showed that the time to onset of sensory block in L1 was 14.87±3.1 minutes in group of patients receiving l8 ml solution containing bupivacaine 0.5% and lidocaine 2% in a 1: 1 ratio (group I) and 17.12±2.18 minutes in group of patients receiving a total of 18 ml plain 0.5% bupivacaine (group II) (P=0.025). And in their study time to onset of sensory block in T10 was 21±3.37 minutes in group I and 24.9±2.54 minutes in group II (P=0.001). Similarly, according to Brown (2000)[12] onset time of epidurally administered local anesthetic bupivacaine 0.5-0.75% is 20 minutes. The effect of which can be potentiated with the use of adjuvants causing early onset and prolonged effect as compared to bupivacaine alone.

Results of our study also corroborated with the above statement as addition of epidural ketamine to bupivacaine caused early onset of analgesia with prolongation of effect.

In similar to our results,Noha Sayed Hussien, (2011)[13] summarised that Magnesium also causes an early onset of analgesia by comparing magnesium sulphate and clonidine as adjuvants to epidural anesthesia in patients undergoing abdominal hysterectomies and concluding that co-administration of magnesium sulphate with epidural bupivacaine produces predictable rapid onset of anesthesia without any side-effects .Similarly Ghatak T (2010)[14] evaluated the effect of Magnesium

Sulphate Vs Clonidine as an Adjunct to Epidural Bupivacaine and showed that Time to achieve T6 block was least in epidural magnesium adjuvant group (11.80 ± 3.21 minutes) and highest (18.73 ± 2.79 minutes) in control group, whereas it was 16.93 ± 3.43minutes in clonidine group of patients. The difference between the groups was statistically significant.

In our study, adding Ketamine and magnesium as adjuvant prolonged analgesic effect were seen for longer duration. Magnesium as an adjuvant were found to have prolonged analgesic effect as compared to plain bupivacaine group alone. This result was further supported by a study done by Riham Hasanein in 2012.[15] They studied epidural magnesium sulfate as an adjuvant to bupivacaine and fentanyl for labor analgesia and concluded that Magnesium sulfate added to bupivacaine and fentanyl for labor epidural analgesia resulted in faster onset, and longer duration of action. Similarly Paolo Feltracco(2013)[16] did a study whose the findings also similar to the findings of our study. They showed that epidural infusion of subanesthetic doses of S(+)- ketamine during thoracic surgery provides better postoperative analgesia than epidural ropivacaine. VAS and Cumulative fentanyl consumption during surgery was significantly lower in ketamine group as compared to ropivacaine. Similarly Pilar Taura (2002)[17] showed that 20 or 30 mg of ketamine administered epidurally enhances the analgesic effect of epidural morphine, and significantly reduces the need for complementary analgesia.

Though magnesium also provided a good pain relief it was statistically lower as compared to ketamine. Earlier studies of magnesium were done compared other adjuvants and not with ketamine as done in our study. Similar complications like bradycardia and hypotension were also found in a study done by Dong-Youp Han (2010).[18] They enrolled ninety three patient scheduled for TURP under epidural anesthesia and divided them into three groups. They administered epidurally0.75% ropivacaine in Group 1, 0.75% ropivacaine plus ketamine(.2mg/kg)in group 2 and 0.75% ropivacaine plus ketamine (0.4mg/kg) in group 3 and they found that Systolic and diastolic arterial pressure and heart rate were significantly lower in group 1 than in the other groups, but there was no significant difference in hemodynamic change between group 2 and group 3. They concluded that hypotension and, bradycardia, were significantly higher in group 1 than in the other groups. There were no significant differences in side effects between group 2 and group 3. Shivering occurred in 7(23.3%) patient in group I only and no patients in group II and group III suffered from shivering during this study. This could be explained by a study done by Dong-Youp Han (2010)] who found that epidural ketamine 0.2 mg/kg and 0.4 mg/kg lowered incidence of shivering and concluded that prophylactic use of low-dose epidural ketamine would be helpful in preventing any adverse effects, including shivering. Supporting its role, a study done by Noha Sayed Hussien in (2011).They showed that no patient in magnesium bupivacaine group suffered from shivering where as five patient in plain bupivacaine group and eight patient in bupivacaine+ clonidine group suffered from shivering.

No other complications were reported in our study. No psychomimetics effect were found in any patient during study. Paolo Feltracco, (2013) [21]stated that no patients experienced psychotomimetic side effects with epidural use of ketamine as associated with its intravenous route.

After comparing the 3 groups in our study in terms of hemodynamic stability, onset and duration of analgesia, VAS scores and complication, following inferences were drawn. Epidural anaesthesia provides stable hemodynamics and prolonged post operative pain relief as compared to general anaesthesia in abdominal surgeries. Better analgesia with less VAS score, less requirement of perioperative analgesic consumption, early onset with increased duration of first top up, and fewer incidence of adverse effect were seen in ketamine group as compared to magnesium group or plain bupivacaine group. The clinical and pharmacological properties of magnesium group were found to be intermediate in between the above mentioned two groups.
Limitations of our study are that we have not included patients of ASA III and IV, therefore results of this study cannot be applied completely on them. Decision should be taken on individual basis. Also Sample size of the study was not adequate to reflect pharmacological properties of study drug in general population and person to person variation may exist. Hence to confirm our findings further more studies with larger number of patients may be suggested.

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