COMPARISON OF EFFECT OF MAGNESIUM SULPHATE AND PRESERVATIVE-FREE KETAMINE AS AN ADJUNCT TO EPIDURAL BUPIVACAINE FOR POSTOPERATIVE ANALGESIA IN ABDOMINAL HYSTERECTOMY

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ABSTRACT

BACKGROUND

Neuraxial blocks are the most common method of anaesthesia in abdominal hysterectomies and epidural technique has been used widely to provide both anaesthesia and postoperative analgesia. It has become a common practice to use polypharmacy approach for treatment of intra and postoperative pain, because no drug has yet been identified that specifically inhibit nociception without side effects.

The aim of the study is to compare the effects of magnesium sulphate versus preservative-free ketamine as an adjunct to epidural bupivacaine for postoperative analgesia in abdominal hysterectomy.

MATERIALS AND METHODS

After obtaining informed consent, the patients were divided into 3 groups of 40 each to receive 20 mL 0.5% bupivacaine (group B), 19 mL 0.5% bupivacaine + 50 mg magnesium sulphate (group BM), 19 mL 0.5% bupivacaine + 50 mg preservative-free ketamine (group BK). Epidural catheter was inserted at L_1-L_2 space using standard technique. Correct placement was confirmed by a test dose of 2% lignocaine + adrenaline 1 in 2 lakhs. Postoperative analgesia were assessed by VAS score and 0.125% bupivacaine infusion and 1 g paracetamol IV infusion was given as rescue analgesics when VAS ≥4. Onset duration, motor block and side effects were also monitored.

RESULTS

Mean time of duration of onset in group B, BM, BK were 20, 14, 18 minutes, respectively. Mean time for rescue analgesia were 180, 240 and 480 minutes in group 1, 2 and 3, respectively. These differences were statistically significant. The side effects noticed in each group were not statistically significant.

CONCLUSION

The onset of effect is faster when magnesium sulphate were added as an adjunct to bupivacaine as compared to preservative-free ketamine. The postoperative analgesia is found to be more with preservative-free ketamine as compared to magnesium sulphate without any significant side effects.

KEYWORDS

Epidural, Magnesium Sulphate, Preservative-Free Ketamine, Bupivacaine, Postoperative Analgesia, Abdominal Hysterectomy.

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BACKGROUND

Epidural anaesthesia is being considered as a good and relatively inexpensive technique for providing surgical anaesthesia and postoperative analgesia. It is also useful in preventing operative pain by blunting somatic, endocrine and autonomic responses of pain.

A polypharmacy approach has been used for treatment of intra and postoperative pain because no drug has yet been identified as superior in preventing nociception without associated side effects.[1]Research continues concerning multiple techniques and different drugs that may provide better surgical anaesthesia and postoperative pain relief. Magnesium is the second most plentiful intracellular cation in our body. It is said to have antinociceptive effects in animal and human models of pain.[2] A systematic review mention that it may be worthwhile to further study the role of adding magnesium sulphate in providing postoperative analgesia, because it is a relatively harmless adjuvant, not so expensive and it also have promising antinociceptive effect.[3] The primary mechanism is based on the physiological antagonism of calcium ion by regulating the voltage dependent regulation of calcium influx into the cells.

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Magnesium also have noncompetitive antagonism of N-methyl-D-aspartate receptors, which potentiates its antinociceptive action.[1]

Ketamine is an anaesthetic agent with a wide range of applications in anaesthesia. It has a variety of mechanisms for analgesia. It produces analgesia by binding noncompetitively to a subset of glutamate receptors stimulated by the excitatory amine NMDA. Blocking this leads to a decrease in stimulation of dorsal horn neurons. These receptors are located in the brain as well as in the substantia gelatinosa of spinal cord. They play an important role in central processing of pain and in neural plasticity in the spinal cord.[4]

There are only limited studies, which compare the effects of magnesium sulphate and preservative-free ketamine administered epidurally as an adjunct to epidural bupivacaine for postoperative analgesia. Both ketamine and magnesium are NMDA receptor antagonists, which have a variety of effects when used as adjuncts in epidural analgesia. We therefore conducted a prospective observational cohort study to compare the effects of magnesium sulphate versus preservative-free ketamine coadministered epidurally as adjunct to epidural bupivacaine for postoperative analgesia. In small doses, magnesium sulphate is not associated with any major side effects. Preservative-free ketamine is also without any major adverse effects.

Aims and Objectives

To evaluate the effect of adding magnesium sulphate versus preservative-free ketamine as an adjunct to epidural bupivacaine for postoperative analgesia in abdominal hysterectomy.

MATERIALS AND METHODS

After obtaining approval of the hospital ethics committee and written informed consent from patients, 120 American Society of Anesthesiologist Physical Status class I and class II females in the age group of 35-65 years posted for abdominal hysterectomy under epidural anaesthesia were included in this prospective comparative randomised study. Patients not willing for neuraxial block, who took analgesics within 24 hours, any history of allergy to drugs in the study design were excluded from the study.

They were divided into 3 groups, each group consisting of 40 subjects. In group B patients (n=40), 19 mL 0.5% bupivacaine + 1 mL normal saline, in group BM patients (n=40), 19 mL 0.5% bupivacaine + 50 mg MgSO4 (using insulin syringe) diluted to 1 mL with normal saline in group BK (n=40) 19 mL 0.5% bupivacaine + 50 mg preservative-free ketamine were given epidurally for surgical anaesthesia and postoperative analgesia. After fasting for 8 hours, Tab. Alprazolam 0.5 mg HS day before surgery given. Tab. Ranitidine 150 mg HS on preoperative day and morning of surgery given. 18 gauge intravenous access, preferably on nondominant forearm/hand obtained. All patients were preloaded with normal saline 10 mL/kg. Epidural catheter inserted under strict asepsis under local anaesthesia at L1-L2 epidural space using standard technique. Correct placement of catheter was verified with a test dose of 3 mL 2% lignocaine with 1:2 lakh adrenaline. Intraoperatively, NIBP, ECG and pulse oximetry were assessed every 5 minutes till the end of the surgery and every 15 minutes in the first postoperative hour followed by every 30 minutes for the next 3 hours. 20 mL of drug will be given epidurally in incremental dose. Sensory blockade will be assessed bilaterally by analgesia to pinprick with short hypodermic needle in the midclavicular line. Motor blockade will be assessed by modified Bromage scale (0- no motor lock, 1-inability to raise extended leg, able to move knee and feet; 2-inability to raise extended leg and move knee, able to move feet; 3-complete block of motor limb). The level of sensory blockade will be assessed every 2 minutes until maximum level of block is achieved and at 5 minutes interval subsequently. Postoperatively, pain will be assessed by numerical rating score. Score ≥4 is considered painful. Total duration of analgesia will be taken as the time from attainment of T4 level up to first complaint of pain. Bolus 0.125% bupivacaine and elastomeric infusion pump with 0.125% bupivacaine will be given as rescue analgesia. Time for first epidural top up and occurrence of any adverse effect if any will be recorded.

RESULTS

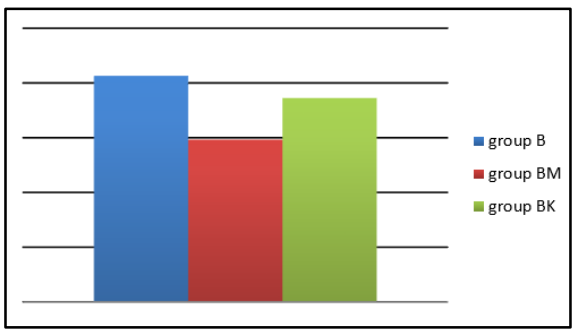
One hundred and twenty subjects included in the study were divided into three groups. All groups received 20 mL local anaesthetic solution epidurally. Group B received 19 mL 0.5% bupivacaine + 1 mL normal saline; Group BM received 19 mL 0.5% bupivacaine + 50 mg magnesium sulphate (using insulin syringe) diluted to 1 mL normal saline; Group BK received 19 mL 0.5% bupivacaine + 50 mg preservative-free ketamine. The statistical analysis was done by ANOVA using the computer software Statistical Package for Social Sciences (SPSS) followed by multiple comparison by Bonferroni. All the three groups were demographically comparable.

Parameter	Group B	Group BM	Group BK	P value
Mean age ± SD	46.78 ± 3.053	51.30 ± 4.767	53.05 ± 5.179	0.933
Mean Weight ± SD	59.35 ± 5.250	55.33 ± 6.518	57.63 ± 6.037	0.093

Table 1. Demographic Parameters (Age and Weight)

Onset of Analgesia

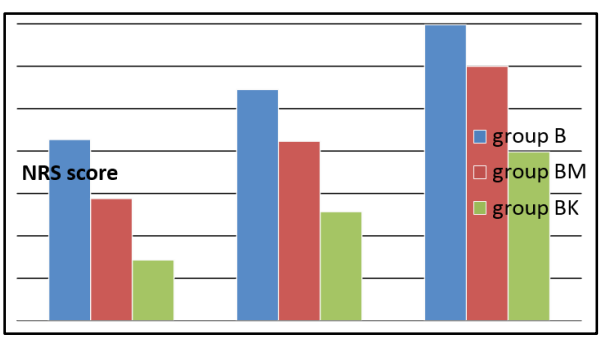
Onset of analgesia was most rapid in Group BM and slowest in Group B. The mean time for onset was 20.63 ± 2.01 minutes in Group B, 14.65 ± 1.76 minutes in Group M and 18.43 ± 2.03 minutes in Group BK. Onset of analgesia was earliest in Group BM and this was statistically significant when compared to Group B ($p<0.001$) and Group BK ($p<0.001$).



Graph 1. Onset of Analgesia

Numerical Rating Scale

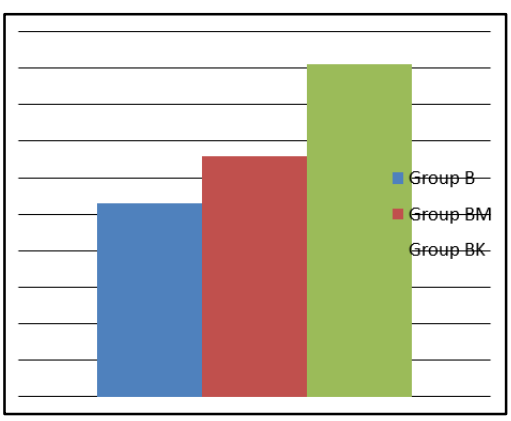
The numerical rating score assess the subjective feeling of pain and denotes the effectiveness of analgesia. The scores were assessed at one hour, three hour, four hour and six hours of postoperative period and found to be less with group BK. The mean NRS scores of group BK at 3, 4, 6 hours were 1.43, 2.57, 3.98, respectively, which was very low when compared to group B and group BM. This was statistically significant when compared to group B (p value <0.001) and group BM (p value <0.001).



Graph 2. Numerical Rating Scale

Total Duration of Analgesia

Total duration of analgesia was taken as the time from attainment of sensory level up to T_4 till the patient complains of pain for the first time. The mean duration of analgesia were 5.3 ± 0.8 hours, 6.6 ± 1.1 hours, and 9.1 ± 1.2 hours in group B, group BM and group BK, respectively. Total duration of analgesia was more with group BK and this was statistically significant when compared to group B (p value <0.001) and group BM (p value <0.001).



Graph 3. Total Duration of Analgesia

Side Effects

There were no major side effects in any of the groups. Vitals were stable in all the groups throughout the procedure. 3 patients in group B and 1 patients in group B had hypotension postoperatively (systolic BP <90). 2 patients in group B and 1 in group BM had bradycardia <50/mt). Six patients in Group BK suffered from altered mentation and 3 patients in Group BM suffered from vomiting. But, all these were not statistically significant. Hypotension managed with intravenous fluids and vomiting managed with Inj. Ondansetron 4 mg IV patients with altered mentation were given psychological assurance.

	Group B	Group BM	Group BK
Hypotension	3	1	0
Bradycardia	2	1	0
Altered mentation	0	0	6
Vomiting	0	3	0

Table 2. Side Effects

Epidural anaesthesia is a commonly used practice for both surgical anaesthesia and postoperative analgesia. Continuous catheter-based infusions of dilute local anaesthetic and other adjuvants are used for postoperative analgesia after major lower limb, abdominal and thoracic surgeries. Moreover, it can reduce cardiovascular and pulmonary complications after major surgeries.[5] Spread of anaesthetic within the epidural space and subsequent block height is related to a variety of factors.[6] Local anaesthetics can be given as a single bolus dose or through continuous epidural catheter. A single bolus can provide surgical anaesthesia ranging from 45 minutes upto 4 hours depending on the type of local anaesthetics and adjuvants. Continuous epidural can provide analgesia for days.

Variety of drugs have been used as adjuvants in epidural analgesia along with local anaesthetic to prolong duration and to increase the depth of anaesthesia. Vasoconstrictors like epinephrine, opioids, alpha 2 agonists, e.t.c. are used as adjuvants. Neostigmine produces prolonged analgesia without causing respiratory depression, hypotension or motor impairement.[7] Midazolam, tramadol and dexamethasone have also been studied. Preservative-free ketamine and magnesium sulfate are two other drugs used as adjuvants in epidural analgesia to prolong postoperative pain.

Magnesium sulphate is found to have analgesic effects, mediated through antagonism of NMDA receptors in the CNS[8] and also related to regulation of calcium influx into the cells.[9] Several small studies investigating the analgesic potency of intravenous magnesium is being published, which shows conflicting results.[10] But, a meta-analysis of all available trials of intravenous administration of magnesium shows reduction of postoperative opioid requirements. Animal studies shows direct intrathecal administration of magnesium increases the antinociceptive effect of opioids. Intrathecal and epidural administration of magnesium also increase the mean duration of analgesia. But, the dose of neuraxial magnesium that produce safe anaesthesia without any major side effects remain unclear. When magnesium is

given epidurally, increase the time to first analgesic request and it was not associated with any major side effects like hypotension, bradycardia or sedation.

Ketamine have analgesic properties, which is also mediated through NMDA receptors. With prolonged repetitive nociceptive stimulation NMDA receptors are activated, releasing excitatory neurotransmitters like glutamate, aspartate and neurokinin. Ketamine acts through antagonism of NMDA receptors located on the secondary afferent in the dorsal horn of spinal cord thus preventing enhancement of excitatory neurotransmission. These neurotransmitters also mediate many activities including central sensitisation, wind up and the plasticity of different actions like memory vision and spinal sensory transmission. Neuraxial and epidural ketamine should be in a preservative-free solution to avoid neurotoxic effects. Combination of epidural ketamine bupivacaine and opioid infusions improved analgesia without increasing side effects. Ketamine has got synergism with dopaminergic, serotoninergic and opioid receptors. It is also effective in treating neuropathic pain. In high doses, it also inhibit descending inhibitory pathways. The main side effects include sedation, headache and transient back pain on injection. No reports of hallucination, respiratory depression or neurologic deficit upto a dose of 1 mg/kg.

Waleed S.H. Farrag, Abdelrady S. Ibrahim, Mostafa Galal Mostafa et al have done a prospective randomised observer blinded study to compare ketamine versus magnesium sulphate with caudal bupivacaine block in paediatric inguinoscrotal surgery. They found that ketamine is safe and effective for paediatric population and have longer postoperative analgesia than magnesium sulphate.[11]

In the present study, it was found that adding preservative-free ketamine to local anaesthetic bupivacaine prolongs the duration of postoperative analgesia as compared to bupivacaine alone. This study also confirms the findings of several previous studies comparing the same drugs.

Deepa Chandramohan, Shirle A d'souza conducted a randomised double-blind study to evaluate the effect of adding 0.5 mg/kg racemic preservative-free ketamine to 0.25% bupivacaine for caudal analgesia in 60 children coming for infraumbilical surgery. They found that ketamine is a safe and effective adjuvant to bupivacaine for prolongation of analgesia in children.[12]

Muge Arikan, Bilge Aslan, Osman Arikan, Eyup Horasanli, Abdulkadir, but conducted a randomised control study to evaluate the effect of magnesium and ketamine on postoperative pain and morphine consumption. 120 subjects were allocated into groups of 40 each randomly and received ketamine 0.2 mg/kg followed by 0.05 mg/kg/hour, magnesium 50 mg/kg followed by 10 mg/kg/hour and normal saline. They found that addition of ketamine prolongs postoperative analgesia and reduces morphine consumption.[13]

Rafael DeRossi, Cassio Tadeu Dias Pompermeyer, Amadeu Batista Silva-Neto, Andrea Lantieri Correa de Barros, Paulo Henrique de Affonseca Jardim, Fabricio Oliveira Frazilio I, conducted a randomised study to compare the effect of lumbosacral epidural magnesium and ketamine for analgesia in conscious sheep. 6 sheeps were given 2.5 mg/kg ketamine, 100 mg magnesium sulphate, 2.5 mg/kg ketamine plus 100 mg magnesium sulphate respectively 2 weeks apart. They have found that analgesia was more with ketamine plus magnesium group. But, ketamine give more prolonged analgesia than magnesium when used alone.[14]

Present study also demonstrate the same results. Preservative-free ketamine and magnesium sulphate prolongs the postoperative analgesia when given epidurally as adjunct to bupivacaine, than bupivacaine is used alone.

Ashraf A. Hassan studied the preemptive analgesic effect of low dose n-methyl-d-aspartate receptor antagonists, ketamine and magnesium in conjunction with spinal anaesthesia. 45 subjects were divided into 3 groups receiving 0.5 mg/kg ketamine, 25 mg/kg magnesium and an equivalent amount of saline 5 minutes prior to spinal anaesthesia intravenously. They found that both ketamine and magnesium potentiates bupivacaine-induced spinal anaesthesia, prolongs duration of analgesia and reduces analgesic requirement.[15]

Nadia Helmy et al conducted a randomised study to compare the preemptive analgesic effect of low-dose ketamine versus magnesium sulphate on parturient undergoing caesarean section under general anaesthesia. 60 subjects were divided into three groups receiving 0.3 mg/kg ketamine, 30 mg/kg magnesium sulphate and normal saline, respectively. They concluded that both reduced the intraoperative fentanyl requirement and ketamine provides better postoperative analgesia.[16]

CONCLUSION

It is concluded from this study that both preservative-free ketamine and magnesium sulphate prolongs the duration of analgesia when used epidurally along with bupivacaine without producing any major side effects. Preservative-free ketamine is a better agent in prolonging the duration of analgesia while magnesium sulphate is better regarding onset of action. Both ketamine and magnesium is not found to have associated with any major side effects.

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