ISSN (O):2395-2822; ISSN (P):2395-2814

Comparative Study of Clonidine and Magnesium Sulfate Used as Adjuvant to Epidural Bupivacaine in Orthopedic Lower Limb Surgery.

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Received: November 2016
Accepted: November 2016

ABSTRACT

Background: A lot of researches have been done to find an ideal adjuvant to bupivacaine in epidural anaesthesia that inhibits intra and post operative pain and prolongs the duration of anaesthesia without any side effects. Study regarding antinociceptive effect of magnesium in epidural route is very limited. **Aim**: This study was done to evaluate the onset, extent and duration of sensory and motor block and side effects of clonidine and magnesium sulfate when used as an adjuvant to bupivacaine in epidural anaesthesia in lower limb orthopedic surgery. **Methods**: A prospective randomized double blind study was conducted on 60 patients of American society of anaesthesiologists status I and II, posted for lower limb orthopedic surgery. All patients were randomly allocated into two groups of 30 each; group I was bupivacaine - clonidine group (BC) and group II was bupivacaine – magnesium sulfate group (BM). Group I (BC) patients received 16 ml of 0.5% bupivacaine and clonidine 2mcg/kg. Group II (BM) patients received 16 ml of 0.5% bupivacaine and magnesium sulfate (50 mg). The onset, extent, duration of sensory and motor blocks and side effects were recorded. **Results:** Magnesium sulfate had a visible edge over clonidine as it enabled an earlier onset of sensory block but duration of analgesia was more in clonidine group. Sedation scores were statistically significant with BC group in comparison to BM group. Both groups were haemodynamically stable in peri and post-operative period. **Conclusion**: Magnesium sulfate was a better alternative to clonidine as an adjuvant to bupivacaine in epidural anaesthesia in orthopedic lower limb surgeries for rapid onset of action but clonidine has prolonged duration of action.

Keywords: Clonidine**,** Magnesium sulfate, Bupivacaine, Orthopedic**.**

INTRODUCTION

Pain is defined by the International Association for Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage[1]. Epidural anaesthesia is a safe and popular technique for surgical anaesthesia as well as for post operative analgesia.

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It has been shown to blunt the stress response to surgery, decrease intraoperative blood loss, reduce the incidence of postoperative thromboembolic events and decrease morbidity and mortality in high-risk surgical patients. It can be used to extend analgesia into postoperative period, providing better analgesia that can be achieved with various adjuvants like opioids and other drugs.[2]

Clonidine has been used as an adjuvant in regional anaesthesia in various route.[3] It is an alpha-2 adrenergic agonist that produces analgesia via a non-opioid mechanism. It is also helpful in sparing local anaesthetic doses, which consequently reduces the incidence of side effects associated with larger doses of these anaesthetics.[4] The combination of epidural clonidine with bupivacaine for analgesia has been extensively studied and it has been shown to improve analgesia. After sodium, potassium and calcium, magnesium is the most abundant cation in our body. It has antinociceptive effects in animal and human models of pain.[5,6] Noxious stimulus produces an influx of calcium ion through both voltage sensitive calcium channels that facilitates presynaptic release of neurotransmitters and post synaptic N-methyl D-aspartate calcium channels which triggers the sequence of events leading to

cellular hyper excitability.[7] Studies in animal models of persistent pain in which central sensitization is present support this theory.[8,9] Magnesium is a relatively harmless molecule and not expensive which may provide perioperative analgesia on the biological basis for its potential anti-nociceptive effect.[10-12] These effects are primarily based on physiological calcium antagonism, that is voltage-dependent regulation of calcium influx into the cell, and noncompetitive antagonism of N-methyl D-aspartate (NMDA) receptors.[13,14]As, there is no ideal adjuvant drug available for perioperative epidural analgesia, the present study was conducted to compare epidural plain bupivacaine with clonidine and plain bupivacaine with magnesium sulphate in patients undergoing elective lower limb surgery in respect of onset and duration of sensory and motor block ,hemodynamic parameters and incidence of side effects.

MATERIALS AND METHODS

After the approval of the Institutional Ethical Committee, randomized double blind, prospective study was done in 60 patients posted for elective lower limb surgery. Patients included in the study were of ASA grade I and II ,age from 20 to 60 years, of either sex and weight 40-70kg. Local infection in the lumbar region, known hyper-sensitivity to amide local anaesthetic, bleeding diathesis, spinal deformity, chronic pain syndromes and known neurological, cardiac, renal, metabolic and psychological disorder were excluded from this study. Randomization was done by a computer derived random number sequence.

Patients were visited on the preoperative day for pre-anaesthetic checkup. Clinical examination of respiratory system, cardiovascular system and central nervous system were done. Vertebral spine was also examined. Laboratory investigations were noted. The patients were explained in detail about the procedure of lumbar epidural block. All their queries and doubts were answered to get their confidence and support. Patients were kept fasting overnight after a light meal. All patients received Tab Alprazolam 0.25 mg orally night before surgery. All patients had an intravenous line with 18G cannula before arriving in the operation theater. After arrival of patients in the operation theater a base line pulse rate, blood pressure, ECG, respiratory rate, SpO_2 were noted. The drugs were prepared by an anaesthesiologist who was not involved in the study. The patients were kept in sitting position. For epidural anaesthesia, 18G Tuohy needle was used. Epidural space (L3-4) was identified by loss of resistance to air technique. After negative aspiration test for blood and CSF, a test dose was administered with 3 ml of inj. Lignocaine hydrochloride 2% with adrenaline (1:200000). After ensuring proper epidural placement of the needle tip, the study drug was slowly injected in small increments with repeated aspiration test as per protocol. After placement of study drug, epidural catheter was introduced. Monitoring of vital signs was continued throughout the procedure. The patients were made supine. No other analgesic was given to the patients intraoperatively. Group BC (n=30) patients received total volume of 16ml (15ml of plain 0.5% bupivacaine + clonidine 2mcg/kg made up to 1ml by adding 0.9% saline. Group BM (n=30) -received a total volume of 16ml (15 ml of 0.5% bupivacaine + 1 ml magnesium sulphate (50 mg). The patients were administered O_2, 3 L/min through facemask. Onset of sensory block was assessed by pinprick method at every minute's interval. Time duration was assessed from local anaesthetic solution injection to epidural space to start of loss of pain sensation to pin prick. Duration of Sensory Block: Assessed every 15 minutes postoperatively by pin prick method[15]. Time duration was assessed from onset of sensory block to regression of dermatome of two segments. Onset of motor block was assessed by modified Bromage scale[16] as follows: 0-no paralysis, 1-inability to raise extended leg. 2-inability to flex knee, 3-Inability to flex ankle joint.

Duration of analgesia was assessed every 15 minutes postoperatively by 10 cm Visual Analogue Scale (VAS) 17. 0 - no pain, 10 - worst possible pain.[17]

Time duration was assessed from onset of sensory block to first request for rescue analgesic or VAS score 5 or more.[18]

Injection Tramadol 2mg/kg was given intravenously as rescue analgesic.

Haemodynamic parameters like Heart rate, Systolic BP, Diastolic BP, Respiratory rate were noted at 0, 15, 30, 60, 75, 90, 120, and at 240 mins from administration of epidural anaesthesia. Side effects like nausea, vomiting, hypotension, sedation, shivering, headache, etc were noted. Sedation was assessed on 5 point sedation scale. 1-awake and alert, 2-arousable to verbal command, 3-arousable to gentle tactile stimulation. 4-arousable to vigorous shaking, 5-unarousable.[19]

Statistical evaluation

Sample size calculation was done by taking duration of analgesia as primary outcome variable of interest. It was estimated that n=26 (recruitment target achieved - n = 30 in each group) will be required per group to detect 60 minutes difference in this parameter with 80% power and 5% probability of Type I error. This calculation assumed a standard deviation of 75 minutes in duration of analgesia. For statistical analysis, raw data entered into a MS Excel spread sheet and analyzed by SPSS 21 (statistical software version 21). Unpaired student's t– test was used to compare normally distributed numerical variables. All analysis were two-tailed and p value <0.05 was taken to be statistically significant.

RESULTS

There was no statistical difference regarding age, sex, weight, height and duration of surgery. [Table 1]

Table 1: Demographic characteristics

Parameters	Group BC (mean±SD)	Group BM (mean±SD)	P value
Mean Age (years)	32.90±7.443	36.433±8.904	0.101
Sex distribution (m/f)	16/14	15/15	0.796
Weight (kg)	56.766±6.871	56.433±7.113	0.854
Height (cm)	155.133±9.000	153.400±10.344	0.491
Duration of surgery (min)	117.166±38.02	127.000±33.77	0.294

Table 2: Epidural block characteristics

Block characteristics	Group BC (mean±SD)	Group BM (mean±SD)	P Value
Onset time of sensory block at T 10 (mins)	8.15±2.84	6.54±2.51	0.0235
Time to max sensory block (mins)	15.74±3.96	12.34±3.75	0.001
Time for complete motor block (mins)	19.14±5.34	15.36±6.81	0.06
Total ephedrine requirement (mg)	7.35±2.1	6.55±1.8	0.11

Time to achieve T10 block was less in BM group than BC group which was statistically significant. Maximum height of sensory block was achieved earlier by group BM than group BC [Table 2], but there were no significant difference between the groups regarding time taken for complete motor block and ephedrine requirement [Table 2].

Table 3: Epidural block characteristics (Post-operatively)

Parameters	Group BC (mean±SD)	Group BM (mean±SD)	P Value
Mean time to two segment regression (mins)	140.64±10.15	130.45±9.76	0.0002
Mean time to sensory regression at S 1(mins)	340.54±35.84	290.18±34.65	0.0001
Mean time to regression to bromage 1 (mins)	280.52±25.44	250.22±28.26	0.0001
Time to first rescue top up (mins)	350.66±25.8	315.18±24.81	0.0001

Time needed for first dose of rescue top up was more in Group BC, which was statistically significant. Similarly mean time for two segment regression, sensory regression to S1, motor regression to bromage score 1 were more in group BC than group BM and all were statistically significant [Table 3].

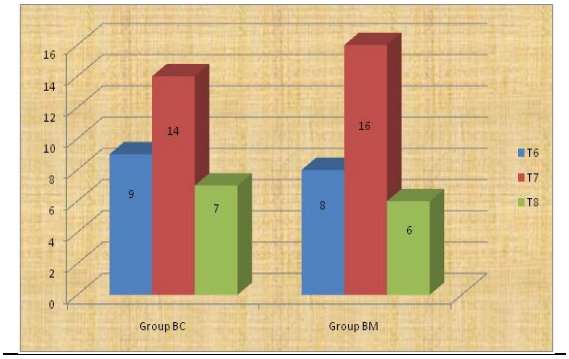

Figure 1: Distribution of block height between study groups

The bar diagram [Figure 1] showing distribution of block height between the groups and it showed no significant differences between the groups.

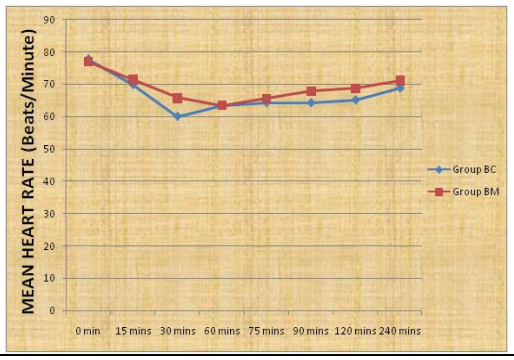

Figure 2: comparison of mean heart rate variability between study groups

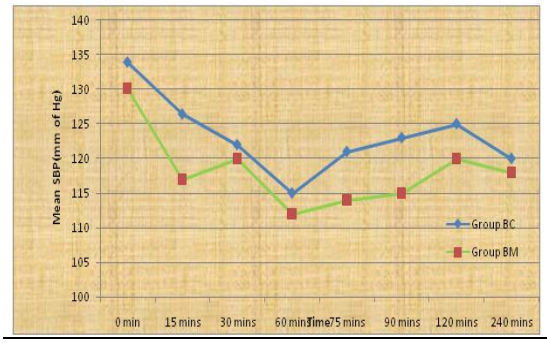

Figure 3: Comparison of mean systolic blood pressure (SBP) variability between study group.

There was no significant deference for hemodynamic parameters between the groups [Figure 2 & 3]

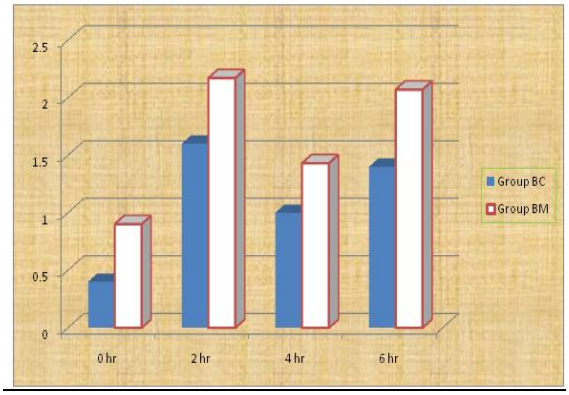

Figure 4: comparison of VAS score between two groups (postoperatively)

Comparison of VAS score had shown between two groups at 0 hr, 2 hr, 4 hr, 6 hr in post operative period [Figure 4]. The VAS was less in 0, 4 and 6 hr in Group BC.

Table 4: Incidence of side effect between two groups

Side Effects	Group Bc	Group Bm	Significance (P Value)
Nausea and vomiting	4 (13.33%)	7(23.33%)	0.317
Shievering	2(6.67%)	4(13.33%)	0.389
Sedation	8(26.66%)	1(3.33%)	0.03
Headache	3(9.99%)	1(3.33%)	0.605

Sedation was significantly high in BC group (26.66%) but there was no significant difference in incidence of other side effects between study groups [Table 4].

DISCUSSION

Previously many drugs have been used as an adjuvant with local anesthetics. The reasonably extensive clinical experience with clonidine reflects the broader experience with alpha2 -adrenergic agonists in regional anaesthesia. Epidural clonidine appears to offer unique advantages over existing adjuvants. Clonidine also produces side effects like hypotension, bradycardia, and sedation.[20]

Till now very few studied magnesium sulfate as an adjuvant to local anaesthetics in epidural anaesthesia. Mechanism of intrathecal $MgSO_4$ is postulated to be supraspinal. However Ko et al concluded that $MgSO_4$ 50mg/kg IV failed to demonstrate an increase in the CSF $MgSO_4$ level. Also they did not found any significant increase in the post-operative analgesia.[21] Bilir et al showed that epidural magnesium sulfate reduces post-operative analgesic requirement. Again the primary mechanism of action of $MgSO_4$ being antagonism of NMDA receptors, it can be postulated that quicker onset and relatively prolonged analgesia of $MgSO_4$ with bupivacaine may be due to their direct effects on the nerve roots in the epidural space alone.[22]

Ghatak et al showed that addition of magnesium sulphate, a competitive NMDA receptor antagonist as adjuvant to epidural bupivacaine reduces the time of onset of anaesthesia in comparison to clonidine. Both clonidine and magnesium groups were similar in respect to hemodynamic parameters.[23]Their findings were similar to ours. Eisenach et al showed in their study that Clonidine prolongs and intensifies epidural anaesthetics without increasing hypotension during epidural anaesthesia. In his study clonidine has produced hemodynamic stability which was similar to our study.[24]

Riham et al showed that epidural single dose magnesium sulphate when added to bupivacaine in labour analgesia resulted in significantly faster onset and longer duration of action of epidural analgesia compared to bupivacaine and fentanyl combine.[25]

It was observed in the present study that addition of 50mg of $MgSO_4$ to 0.5% bupivacaine administered epidurally reduces the onset of sensory block compared to epidural 0.5% bupivacaine with clonidine, which was statistically significant. There were no significant change in blood pressure, pulse rate and respiratory rate in both groups. There was no significant increase in side effects except sedation. The onset of motor block was comparable in the two groups. Duration of analgesia is significantly high in BC group. VAS score is less in BC group. Vital parameters were well maintained during intraoperatively and postoperative period and no significant difference in vital parameters was seen in the two groups. Sedation was found more in BC group in comparison to BM group, which was statistically significant. Few other minor side effects like nausea, vomiting, and shivering were found in both study groups but they were statistically not significant.

CONCLUSION

Administration of epidural magnesium sulfate with bupivacaine produces predictable rapid onset of surgical anaesthesia without any side-effects but addition of clonidine to epidural bupivacaine produces prolonged duration of anaethesia with negligible side effects except sedation. The results of the present investigation suggest that magnesium sulfate may be an alternative to clonidine as adjuvant to epidural bupivacaine in lower limb surgery.

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How to cite this article: Pradhan A, Nayak MK, Dash T, Pradhan K, Mishra D. Comparative Study of Clonidine and Magnesium Sulfate Used as Adjuvant to Epidural Bupivacaine in Orthopedic Lower Limb Surgery. Ann. Int. Med. Den. Res. 2017; 3(1):AN08-AN12.

Source of Support: Nil, **Conflict of Interest:** None declared