EVALUATION OF THE EFFECT OF MAGNESIUM SULPHATE VS. CLONIDINE AS AN ADJUVANT TO EPIDURAL LEVOPUPIVACAINE IN PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES- A PROSPECTIVE, RANDOMISED AND DOUBLE-BLIND STUDY

M. Prasad Rao¹, T. Ranganath², Ch. Srinivas Rao³, Sandeep Gurugubelli⁴

¹Associate Professor, Department of Anaesthesiology, Rajiv Gandhi Institute of Medical Sciences, Srikakulam.

²Assistant Professor, Department of Anaesthesiology, Rajiv Gandhi Institute of Medical Sciences, Srikakulam.

³Associate Professor, Department of Anaesthesiology, Rajiv Gandhi Institute of Medical Sciences, Srikakulam.

⁴Senior Resident, Department of Anaesthesiology, Rajiv Gandhi Institute of Medical Sciences, Srikakulam.

ABSTRACT

BACKGROUND

Various adjuvants can be added to local anaesthetics and administered in central neuraxial blockade to improve the speed of onset, quality and duration of analgesia with desirable sedation. Magnesium Sulphate and Clonidine are relatively harmless molecules, cost-effective and biological basis for their anti-nociception is promising. Therefore, in this study, Magnesium Sulphate was compared with Clonidine (α_2 -agonist) as adjuvant to Levobupivacaine in epidural anaesthesia.

The aim of the study is to compare the effects of Magnesium Sulphate (50 mg) Vs. Clonidine (150 mcg) as an adjuvant to Epidural 0.5% Levobupivacaine in adult patients undergoing lower abdominal surgeries in a prospective, randomised and double-blinded study.

MATERIALS AND METHODS

Hundred patients undergoing elective lower abdominal surgeries, aged between 18-50 years of either gender, belonging to ASA grade I and II were randomly divided into two groups and were subjected to epidural catheterisation with 16/18 G size and given epidural anaesthesia. Group LM- Consists of patients in whom 19 mL of 0.5% Levobupivacaine with Inj. Magnesium Sulphate – 50 mg (in 1 mL) was administered. Group LC- This group comprises of patients in whom 19 mL of 0.5% Levobupivacaine with Inj. Clonidine 150 μ g (in 1 mL) was administered.

RESULTS

The mean time of onset of sensory and motor blockade in Magnesium Sulphate group is significantly less than that of Clonidine group. The duration of sensory blockade and post-operative analgesia was significantly prolonged in Clonidine group than that of Magnesium Sulphate group. Both the groups were similar in haemodynamic stability and side effects.

CONCLUSION

Addition of Magnesium Sulphate to epidural Levobupivacaine produced rapid onset and longer duration of post-operative analgesia with stable haemodynamics, minimal side effects and without any sedation. Addition of Clonidine to epidural Levobupivacaine produced significantly longer duration of analgesia when compared to Magnesium Sulphate but with sedation and fewer side effects.

KEYWORDS

Magnesium Sulphate, Levobupivacaine, Clonidine, Epidural.

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BACKGROUND

Central neuraxial blockade is the commonly used anaesthetic technique for lower abdominal surgeries. Epidural anaesthesia is preferred to spinal anaesthesia because of the advantages like desired segmental blockade, gradual haemodynamic changes, graded level of analgesia and provision of post-operative analgesia. Epidural anaesthesia reduces the peri-operative stress response to surgery and improves surgical outcome.¹

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Corresponding Author:

M. Prasad Rao,

16-1-21, Lakshmi Villa,

Flat No.101, Maharanipeta,

Visakhapatnam-530002.

E-mail: prasadmanem79@gmail.com

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Adjuvants are pharmacological drugs, when co-administered with local anaesthetic agents, may improve the speed of onset, quality and duration of analgesia with desirable sedation. A wide range of drugs have been assessed for both neuraxial and peripheral nerve blocks. Various adjuvants that can be added to local anaesthetics and administered in central neuraxial blockade are opioids, α_2 -agonists, benzodiazepines, neostigmine, ketamine, adrenaline and magnesium sulphate. Sedation, stable haemodynamics and ability to provide smooth and prolonged post-operative analgesia are the main desirable qualities of an adjuvant in neuraxial anaesthesia.

The amide local anaesthetics like Bupivacaine are the most widely used. It is a racemic mixture of the dextro & levo stereoisomers. However, the dextro enantiomer makes Bupivacaine a more cardiotoxic drug. In 1979, Albright² published an alarming editorial in which he associated long-acting local anaesthetic Bupivacaine and Etidocaine with cardiac arrest during regional anaesthesia for Caesarean

section using 0.75% Bupivacaine. Levobupivacaine, the pure S-(-) enantiomer of racemic Bupivacaine, was developed as an alternative to Bupivacaine, to achieve a lower risk of cardiotoxicity. It is associated with a reduced incidence of both cardiovascular and central nervous system toxicity, a concern with racemic Bupivacaine.

Magnesium is the fourth most plentiful cation in our body, having anti-nociceptive effects in animal and human models.³

It is worthwhile to study the role of supplemental magnesium in providing peri-operative analgesia, because it is a relatively harmless molecule, inexpensive and has potential anti-nociceptive effect. The effects are primarily based on physiological calcium antagonism, that is voltage-dependent regulation of calcium influx into the cell, and non-competitive antagonism of N-methyl-D-aspartate (NMDA) receptors.⁴

Clonidine acts as a selective partial agonist of the α -2 receptor with a ratio of 200:1 (α 2 to α 1). The mechanism of action involves activation of α -2 adrenoceptors which reduce peripheral nor-epinephrine (NE) release by a negative feedback mechanism. Stimulation of central α -2 receptors activate noradrenergic imidazoline receptors and also act on descending inhibitory tracts. The overall effect is sympatholysis resulting in analgesia, hypotension, bradycardia and sedation. Thus, decreased activity of second-order neurons and wide dynamic range neurons in the dorsal horn occurs, which in turn attenuates the input from peripheral nociceptive A δ and C fibres.⁵

This study is done to evaluate whether Magnesium Sulphate Vs. Clonidine with Levobupivacaine can improve the quality and increase the duration of epidural anaesthesia or not.

MATERIALS AND METHODS

After approval from the ethics committee of Government General Hospital, Kakinada and taking written informed consent, patients undergoing elective lower abdominal surgeries were included in this prospective, randomised double-blinded study. Patients with ASA grade I and II physical status, aged between 18-50 years, weight <80 kg of either sex were included. Patients with emergency surgery, deformities of the spine, hypersensitivity to any of the drugs in the study, bleeding diathesis, heart block/dysrhythmia and on therapy with Adrenergic Receptor Antagonist, Calcium Channel Blocker or ACE Inhibitor were excluded from the study.

From T.Ghatak⁶ et al study, assuming a one-sided hypothesis and mean difference of duration of analgesia of 19 minutes with an effect size of 0.64, at a power of 90 percent and an alpha error of 5 percent, the sample size obtained for each group was 42. Patients were divided into two groups of 50 each by using simple randomisation technique. Initially random numbers were obtained using Microsoft excel spread sheet and the sequence of random numbers obtained were kept in an opaque envelope secretly so that blinding is maintained. Later recruiting into groups was done based on serial numbers matched with random numbers. Let us assume that we pointed at row 9 at an intersection of column 2. If the number corresponding to it is 55203. Every odd number is assigned to Group A and every even number is assigned to Group B. So the first, second in the sequence are odd numbers and he/she will be assigned to the Group A. As

the third one in the sequence is an even number, he/she will be assigned to the Group B. Similarly, all the patients were assigned and all investigators were kept unaware of the envelope details throughout the whole study period.

During pre-anaesthetic evaluation, patient's detailed history, general physical examination and systemic examination were carried out. Basic demographic data like age, sex, height and weight were recorded, the linear visual analogue scale (VAS) was explained to all patients using 10 cm scale.

All the patients were pre-medicated with 0.05 mg/kg midazolam IM 1 hour prior to the procedure. The pulse rate, respiratory rate, blood pressure and SpO₂ were recorded before starting the case. Peripheral venous cannulation was done with 18 G IV cannula and all the patients were preloaded with 10 mL/kg Ringer Lactate solution. The patients were placed in left lateral position and under strict aseptic precautions. After local infiltration with 1% Lignocaine hydrochloride, the epidural space was identified with an 18/16 G Tuohy needle at L3-L4 interspace, by "loss of resistance" technique. 18/16 G epidural catheter was threaded through the needle in to the epidural space for 3-4 cm and secured with adhesive tapes to the back. After negative aspiration for blood and CSF, 3 mL of 2% Lignocaine with 15 μ g of adrenaline was given as test dose and the patient was turned to supine position. After 5 min., if there is no adverse reaction for the test dose, intravascular and intrathecal placement were ruled out and the study drugs were administered.

Group LM

Subjects (n=50) were given 19 mL of 0.5% Levobupivacaine with Inj. Magnesium Sulphate 50 mg (in 1 mL) administered epidurally.

Group LC

Subjects (n=50) were given 19 mL of 0.5% Levobupivacaine with Inj. Clonidine 150 μ g (in 1 mL) administered epidurally.

The level of sensory block was assessed by bilateral pinprick method, quality of motor blockade assessed by Modified Bromage Scale at 5, 10, 15, 20, 25, 30 minutes intervals. Time of injection was recorded as 0 hour. In the two groups, the following are noted: the onset of sensory blockade at T10 level, maximum sensory level achieved, time to attain maximum sensory level, onset of motor blockade, two segment regression time, duration of sensory block, duration of motor block, duration of analgesia, continuous SpO₂, respiratory rate, heart rate. Haemodynamic variables like systolic BP, diastolic BP, Mean Arterial Pressure, Heart Rate were recorded every 5 min. until 30 min. and at 15 min. interval thereafter up to 90 min. and then at 30 min. interval till the end of surgery. Sedation scores were recorded just before the initiation of surgery and thereafter every 20 minutes during surgical procedure by Observer Assessment of Alertness and Sedation Scale. Side effects like nausea, vomiting, bradycardia, hypotension, respiratory depression, and shivering were noted in both groups. Onset of sensory blockade is taken from the completion of injection of study drug until the patient is not able to feel the pin prick. Onset of motor blockade is taken from the completion of injection of

study drug until the patient is not able to move feet. Duration of motor blockade is taken from the completion of injection of study drug till motor block regresses to Bromage scale 1. Duration of sensory block is taken from the completion of injection of study drug till sensory block regression to T12 dermatomal level. Duration of analgesia is taken from the completion of injection of study drug till the patient has VAS (Visual Analogue Scale) score ≥ 4 . If there was fall in blood pressure more than 30% below the baseline value, even after intravenous fluids administration, Inj. Mephentermine was given in titrated doses. If the pulse rate was less than 30% of baseline, Inj. Atropine 0.6 mg IV was given. If respiratory rate was less than 10/min., respiratory depression was diagnosed.

At the end of the surgery, the patients were shifted to post-operative ward, monitored for every 30 min. for the first six hours and thereafter every hour for 24 hours period. Pain was managed with top up of 10 mL of 0.125% Levobupivacaine.

Statistical Analysis

At the end of the study, all the data is compiled and statistically analysed using SPSS (Statistical Packages for Social Sciences) version 16, parametric data is presented as Mean $\pm$ Standard Deviation and unpaired "t" test is used after considering the normal distribution. Chi-Square test is done to compare the side effects. P value of less than 0.05 is considered statistically significant.

RESULTS

The groups were comparable with respect to age, height, and weight. The time of onset of sensory blockade to T10, time to maximum sensory level and time to onset of motor blockade was less for group LM than that of group LC which is statistically significant. The mean duration of sensory blockade, motor blockade and post-operative analgesia were higher in group LC than that of group LM which is statistically significant. Mean arterial pressure and side effects were comparable as shown in Graph-1 and Table-2 below.

	LM	LC	p value
Age(yrs.)	38.44 $\pm$ 7.08	38.26 $\pm$ 9.13	>0.05
Height(cm)	156.44 $\pm$ 4.20	157.16 $\pm$ 6.10	>0.05
Sensory Onset to T10 (min.)	7.96 $\pm$ 2.18	9.5 $\pm$ 2.61	<0.05*
Time To Maximum Sensory Level(min.)	12.14 $\pm$ 4.28	15.48 $\pm$ 5.21	<0.05*
Two Segment Regression Time(min.)	136.41 $\pm$ 11.80	139.38 $\pm$ 14.68	>0.05
Duration of Sensory Blockade(min.)	218.3 $\pm$ 12.31	242.9 $\pm$ 15.34	<0.05*
Onset of Motor Blockade(min.)	19.5 $\pm$ 2.6	20.94 $\pm$ 2.65	<0.05*
Duration of Motor Blockade(min.)	198.1 $\pm$ 11.45	214.4 $\pm$ 13.2	<0.05*
Duration of Analgesia(min.)	264.22 $\pm$ 16.25	305.04 $\pm$ 16.44	<0.001**

Table 1. Demographic Data and Characteristics of Sensory and Motor Block

*significant **highly significant

Graph 1. Comparison of Mean of MAP at Different Durations

Side Effects	Group LM	Group LC	Chi Square test	*P value
Bradycardia %	3 6%	9 18%	3.40	0.12
Hypotension %	5 10%	10 20%	1.32	0.26
Nausea %	4 8%	10 20%	2.99	0.14
Vomiting %	1 2%	4 8%	1.89	0.36
Shivering %	0	3 6%	-	-
Resp. depression %	0	0	-	-
Dry mouth %	0	5 10%	-	-

Table 2. Comparison of Side Effects

DISCUSSION

Levobupivacaine, the isolated S (-) enantiomer of Bupivacaine, has been shown to be less cardiotoxic than Bupivacaine in pre-clinical studies.^{7,8} The decreased toxicity of Levobupivacaine is attributed to its faster protein binding rate.⁹ Owing to the lower affinity of the S (-) isomer to the cardiac sodium channels compared to the R (+) isomer, it is associated with less cardiac side effects.^{10,11}

Arcioni et al¹² observed that intrathecal and epidural Magnesium Sulphate potentiated and prolonged motor block. They concluded that patients undergoing orthopaedic surgery, supplementation of spinal anaesthesia with combined intrathecal and epidural MgSO₄ significantly reduces post-operative analgesic requirements. Magnesium blocks NMDA channels in a voltage-dependent way and produces a dramatic reduction of NMDA-induced currents.

Clonidine, an alpha-2 agonist induces dose dependent anti-nociception mainly through stimulation of alpha-2 adrenoceptors in dorsal horn mimicking activation of descending inhibitory pathways.¹³ Epidural Clonidine can prolong sensory block to a greater extent than motor block. The mechanism appears to be mediated by the opening of potassium channels and subsequent membrane hyperpolarisation rather than an α 2-agonist effect. The addition of Clonidine reduces both epidural local anaesthetic and opioid requirements.

In a study conducted by Ghatak et al,⁶ epidural Magnesium Sulphate versus Clonidine with Bupivacaine showed that mean time of onset to T6 level for Magnesium Sulphate 11.80 $\pm$ 3.21 min. Vs. Clonidine 16.93 $\pm$ 3.43 min. Vs.

plain Bupivacaine 18.73 ± 2.79 min. ($p < 0.001$), which is comparable to our study.

In this study, the two segment regression time in group LM was significantly less than group LC (group LM 136.44 ± 11 min. Vs. group LC 139.38 ± 14.68 min.). This finding also correlated with the abovementioned study by Ghatak et al⁶ (Magnesium Sulphate 130.33 ± 33.94 min. Vs. Clonidine 145.33 ± 27.74 min.).

The mean duration of sensory blockade in our study was significantly higher with group LC than group LM (Clonidine 242.1 ± 15.34 min. Vs. Magnesium Sulphate 218.3 ± 12.3 min.). In a study conducted by Alves JC, Braz JR,¹⁴ epidural Clonidine with Ropivacaine significantly prolonged sensory, motor and post-operative analgesia ($p < 0.001$), when compared to Ropivacaine alone.

In a study conducted by Khalili G and Janghorbini et al,¹⁵ who compared Magnesium Sulphate with Bupivacaine Vs. plain Bupivacaine for lower extremity surgeries concluded that the duration of sensory blockade was significantly longer with Magnesium Sulphate group than in control group (magnesium sulphate 106.5 min. vs. control group 85.5 min., $p < 0.001$), similar to our study.

Shukla D, Verma A et al¹⁶ in their comparative study of intrathecal Dexmedetomidine and Magnesium Sulphate used as an adjuvant to 0.5% Bupivacaine showed that the duration of analgesia was significantly prolonged in Magnesium Sulphate group as compared to that of control group but to a lesser degree than in the Dexmedetomidine group.

In a study conducted by Bilir A, Gulec S et al,¹⁷ the addition of Magnesium Sulphate as an adjuvant to epidural Fentanyl Bupivacaine concluded that patients with Magnesium Sulphate-Fentanyl group had less pain score in the post-operative period and significantly less cumulative fentanyl consumption in the first 24 hours than in the fentanyl group alone [Magnesium Sulphate-Fentanyl 328 ± 121 mcg Vs. Fentanyl 437 ± 110 mcg (0.05)].

In a study conducted by Wasim Mohammad,¹⁸ Shafat A. Mir et al, the initial epidural dose was least and first dose of rescue analgesia was the longest in Clonidine group followed by the Magnesium group.

In this study, the intra-operative haemodynamic variables were more or less comparable in both the groups except for a few cases in group LC who had transient bradycardia ($n=9$) and hypotension ($n=10$) which are not statistically significant. In group LM, only 3 patients had bradycardia and 5 patients had hypotension. Bradycardia was treated with Inj. Atropine and hypotension was treated with crystalloid boluses and Inj. Mephentermine if needed.

Five patients of group LC had dry mouth, Clonidine is associated with dry mouth in various studies as discussed previously.

Nausea and vomiting was found in few patients which is statistically insignificant. Four patients of group LM and ten patients of group LC had nausea and one patient of group LM and four patients of group LC had vomiting. However, vomiting was treated with Inj. Ondansetron 4 mg ruling out and correcting hypotension which may cause the same.

In group LM, no patient suffered from shivering during the study whereas in group LC, three patients had shivering which is statistically significant. Peri-operative supplementation of Magnesium decreases the incidence of shivering.

None of the patients in the two groups had respiratory depression.

The results of the present study showed that Magnesium Sulphate may be a useful alternative as an adjuvant to epidural Levobupivacaine.

Results Shown That

1. The mean time of onset of sensory and motor blockade in Magnesium group was significantly less than that of Clonidine group.
2. The duration of sensory blockade and post-operative analgesia was significantly prolonged in Clonidine group than that of Magnesium group.
3. Both the groups were similar in haemodynamic stability and side effects.

To conclude, addition of Magnesium Sulphate to epidural Levobupivacaine produced rapid onset and longer duration of post-operative analgesia with stable haemodynamics, minimal side effects and without any sedation, while addition of Clonidine to epidural Levobupivacaine produced significantly longer duration of analgesia when compared to that of Magnesium Sulphate but with sedation and fewer side effects. This study suggests Magnesium Sulphate as a promising alternative adjuvant to neuraxial local anaesthetics.

CONCLUSION

Provision of clinically effective and satisfactory intra-operative and post-operative analgesia is important because of the deleterious effects of pain on various organ systems and its negative input on post-operative recovery. Regional anaesthesia is an excellent choice which provides effective peri-operative analgesia with a single technique due to the availability of long-acting amide local anaesthetics like Levobupivacaine and by the adjuvants like Clonidine and Magnesium Sulphate.

Hence, in this study the effects of Magnesium Sulphate (50 mg) and Clonidine (150 mcg) as an adjuvant to epidural 0.5% Levobupivacaine were studied.

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