DOI: 10.14260/jemds/2015/1359

ORIGINAL ARTICLE

A PROSPECTIVE, DOUBLE BLIND RANDOMIZED CONTROLLED STUDY COMPARING THE EFFECTS OF MAGNESIUM SULPHATE VERSUS CLONIDINE AS AN ADJUNCT TO BUPIVICAINE IN SUB UMBILICAL SURGERIES

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HOW TO CITE THIS ARTICLE:
Sadhana Roy, Mrinalini, A. Sowmya Sri. "A Prospective, Double Blind Randomized Controlled Study Comparing the Effects of Magnesium Sulphate versus Clonidine as an Adjunct to Bupivicaine in Sub Umbilical Surgeries". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 54, July 06; Page: 9358-9369, DOI: 10.14260/jemds/2015/1359

ABSTRACT: OBJECTIVE: Providing comfort to the patient by prevention/relief of pain using various combinations of drugs thus achieving maximal benefit with minimal adverse effects is the ultimate goal of the anesthesiologist in the peri-operative period. **AIM OF STUDY:** To evaluate the efficacy of Magnesium Sulphate Versus Clonidine as an adjunct to Bupivicaine in Epidural Analgesia. **METHODS:** A total of 90 patients of either gender with ASA Grade (I, II), aged between 18 to 60 years scheduled for elective sub umbilical surgeries were randomly assigned in a prospective double blind study to three separate groups that received epidural 0.5% Bupivicaine (19ml) with 1ml of 0.9% Normal Saline or 0.5% Bupivicaine (19ml) with Magnesium sulphate 50mg (1ml) or 0.5% Bupivicaine With Clonidine 150 micro gram (1ml). All Patients were administered Pre-medication as per Hospital Protocol night before and morning of Surgery. Intra operative monitoring of patients included Heart-rate, ECG, SPO2, NIBP, RR as a Base Line and follow-up after Injection of assigned drug. Sensory blockade was evaluated by using bilateral pinprick method, motor blockade was estimated using modified Bromage scale at 5, 10, 15, 20, 25 and 30 Minutes Interval after Epidural Administration of drug. Pain perceived was assessed with Visual Analog Scale (VAS 0 - 10) both Intra Operatively and Post Operatively. In the event of pain with VAS >5, top-up of 0.5% Bupivicaine alone was added. The time from onset of blockade till need for 1st top-up was evaluated. **CONCLUSION:** Co- administration of Magnesium Sulphate (50mg) to Epidural 0.5% Bupivicaine provides a predictable and rapid onset of nerve blockade without any side effects whereas co-administration of clonidine (150 micro-grams) to Epidural 0.5% Bupivacaine produced prolonged duration of anesthesia. The use of adjuvants in Epidural Aneasthesia gives a scope to improve the quality of anesthesia while minimizing the adverse effects.

KEYWORDS: Bupivicaine, Clonidine, Duration, Epidural Anesthesia, Magnesium Sulphate, Onset.

INTRODUCTION: Providing comfort to the patient by prevention/relief of pain and monitoring/maintaining the normal physiology during the peri-operative period is the primary goal of an anaesthetist. Regional anaesthesia and analgesia has the potential to provide excellent operating conditions and prolonged post-operative pain relief. Epidural blockade is becoming one of the safe, inexpensive and most useful and versatile procedures in modern anaesthesiology. It is unique for it can be placed virtually at any level of spine, allowing more flexibility in its application to clinical practice. It is more versatile than spinal anaesthesia, giving the clinician an opportunity to provide anaesthesia and analgesia, as well as enabling chronic pain management. It can also be used to supplement general anaesthesia, thereby providing a more hemodynamically stable operative course. It provides better post-operative pain control and more rapid recovery from surgery.

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However, the effect of analgesia depends on the drug used and its pharmacodynamics. Various combinations of analgesics have been used to titer the analgesic effects focusing on the time of onset and the overall duration of effect with a watchful eye on the side/adverse effects.

Magnesium is the fourth plentiful cation in the body with anti-nocecptive action by competitive inhibition of calcium influx through voltage gated channels and non-competitive antagonism of NMDA receptors.[1]

Clonidine, a centrally acting partial alpha-2 adrenergic agonist inhibits voltage gated sodium channels, suppressing generation of action potentials in the dorsal horns.[2]

This study is an endeavour to find the effect of the drugs as an adjunct to bupivacaine in epidural analgesia, taking cue of blocking different channels in the generation of pain.[3]

MATERIALS AND METHODS: The present study was conducted in Gandhi Medical College/Hospital, Secunderabad, after obtaining the approval from Institutional Ethics Committee and written informed consent from patients. Ninety patients of either gender, with ASA (American society of Anesthesiologists) grade 1 and grade 2, aged between18- 60 years undergoing elective sub umbilical surgeries were enrolled for the study.

The patients with hemodynamic instability, bleeding or coagulation abnormalities, psychiatric diseases, history of drug abuse, allergy to local anesthetics/ clonidine/ magnesium sulphate, local infections at the site of catheter placement and spinal deformities precluding safe procedure were excluded from study.

Patients were randomly allocated to one of the following three treatment groups (n=30 in each group) in a double blinded fashion based on a computer generated code: Group1-patients with epidural 0.5% Bupivacaine (19ml) with 1ml 0.9% normal saline; Group2-patients with epidural 0.5% Bupivacaine (19ml) with Magnesium sulphate 50 mg (1ml); Group3- patients with epidural 0.5% Bupivacaine (19ml) with Clonidine 150 micrograms (1 ml).

All patients were administered pre medications as per hospital protocol, a night before and on the morning of the surgery. Intra operatively monitoring of the patients included heart rate (HR), electrocardiograph (ECG), pulse oximetry (SpO2), non-invasive blood pressure (NIBP), respiratory rate (RR) as a baseline and follow-up after the injection of the assigned drug.

The drug syringes were prepared by a senior anaesthetist and were coded before handing it out to investigator involved in the monitoring the response. Patients were administered epidural block under full aseptic precautions with 18 gauge Touhy needle at the level of L3-4 inter vertebral space with loss of resistance with saline and catheter was secured at 3-4 cm into epidural space and a test dose of 3ml of 2%lignocaine hydrochloride solution containing adrenaline 1: 200, 000 was injected. After 4-6 minutes of administering the test dose, patients in group 1 were injected with19 ml of 0.5%bupivacaine with 1ml of 0.9% normal saline, patients in group2 were injected with 19 ml of 0.5% bupivacaine with 1ml magnesium sulphate (50mg), and patients in group 3 were injected with19ml of 0.5% bupivacaine with 1ml clonidine (150 micrograms).

Patients were monitored with NIBP, HR, ECG, SpO2, RR both intra and postoperatively. Intra and postoperative complications/side effects/adverse effects were recorded and managed according to hospital protocol.

Hypotension (Defined as systolic arterial pressure falling more than 20% mmHg) was treated with inj. mephenteramine 3–6 mg in bolus doses and heart rate <50 beats/min was treated with 0.3 mg of inj. atropine. Intravenous fluids were given as per body weight and operative loss requirement.

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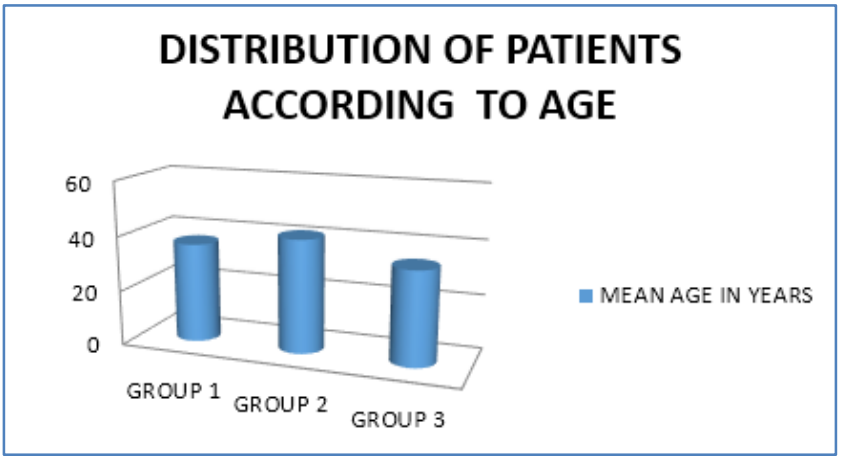
During the surgical procedure, adverse event like anxiety, nausea, vomiting, pruritis, shivering, etc. were recorded. Nausea and vomiting was treated with 6 mg of intravenous ondansetron.

Sensory blockade was evaluated using the bilateral pin-prick method(ref) will be used to evaluate sensory blockade, while motor blockade was estimated using modified Bromage scale(ref) at 5, 10, 15, 20, 25 & 30 minutes intervals after the epidural administration of the drugs.

The surgical position was made after establishment of sensory and motor block. The following block characteristics were observed and recorded- (i) initial period of onset of analgesia, (ii) the highest dermatomal level of sensory analgesia achieved, (iii) the time taken to achieve complete establishment of motor blockade, and (iv) total duration of the effect of analgesia in the three groups.

The patients were informed and educated about the VAS in the pre-operative period, during the pre-anaesthetic checkup while obtaining consent for inclusion in the study, which was a day prior to the day of elective surgery. They were again familiarised with the score before administering the premedications. The pain perceived was assessed with visual analogue scale (VAS, 0-10), both intra operatively and post operatively, starting at 60 minutes of injection of the drug and every 15 minutes subsequently. In the event of pain, with VAS >5, top up of 0.5% bupivacaine alone was added. The time from onset of blockade till the need for first top up was evaluated.

OBSERVATION AND RESULTS: The age distribution among the groups is comparable with mean age in Group 1 being 36.33 years (SD±13.24), Group 2 being 41.30 years (SD±13.759), Group 3 being 34.13 (SD±12.749). There is no significance of age between the groups (p value > 0.05). (Graph 1)



Graph 1: Distribution of patients according to age

The mean weight in group 1 was 62 kg (SD±0.23), in Group 2 was 62.20 kg (SD±8.454), Group 3 was 61.83 kg (SD±.210). All three groups are comparable with no statically significant difference (p>0.05). (Graph 2).

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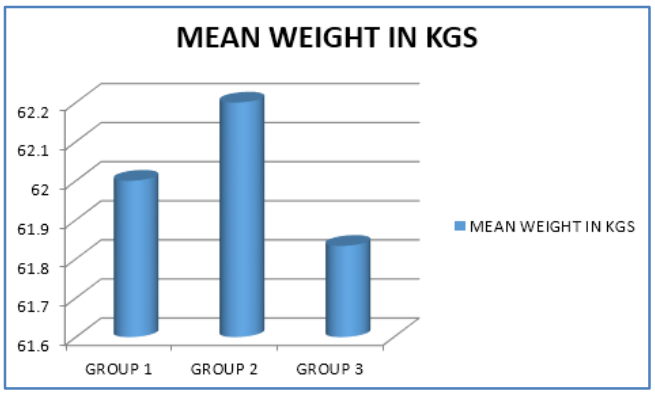
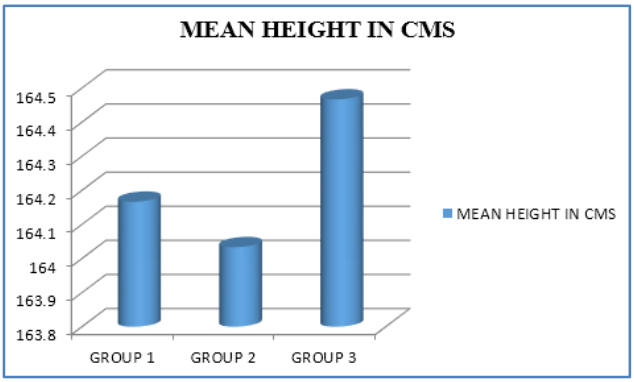


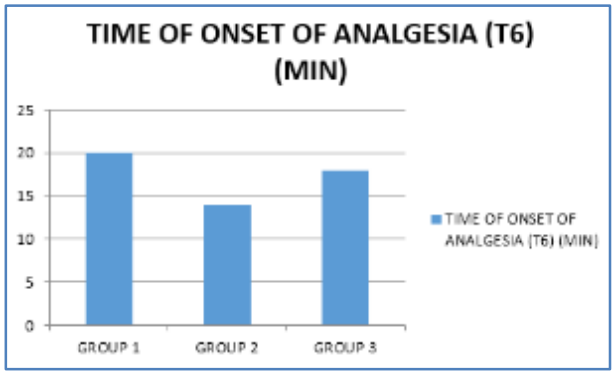
Graph 2: Distribution of patient according to weight

The mean height in Group 1 was 164.17 cms (SD±9.139), in Group 2 was 164.03 (SD±8.612) and in Group 3 was 164.47 (SD±9.350). There was no statistically significant difference between the groups (p >0.05). (Graph 3)



Graph 3: Distribution of patients according to height

There was significant decrease in onset of analgesia in Group 2 (Bupivacaine+$MgSO_4$) as compared to Group 1(Bupivacaine+normal saline) and Group 3 (Bupivacaine+Clonidine). This shows that by addition of Magnesium sulfate to Bupivacaine, there is faster onset of action (p <0.005). (Graph 4).



Graph 4: Time taken to achieve a sensory level of T6

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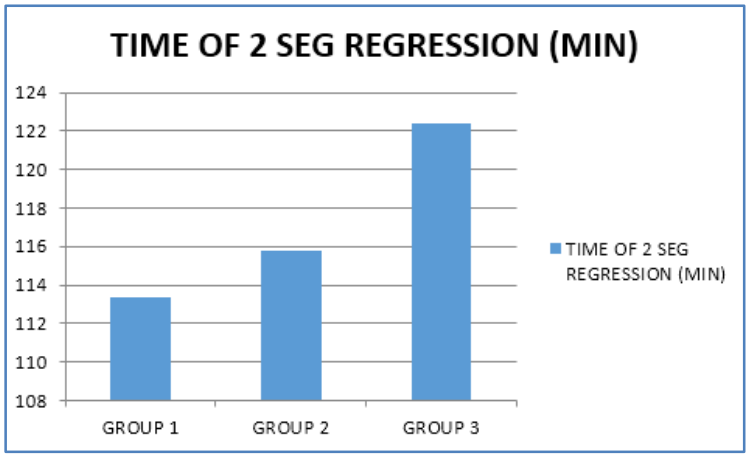
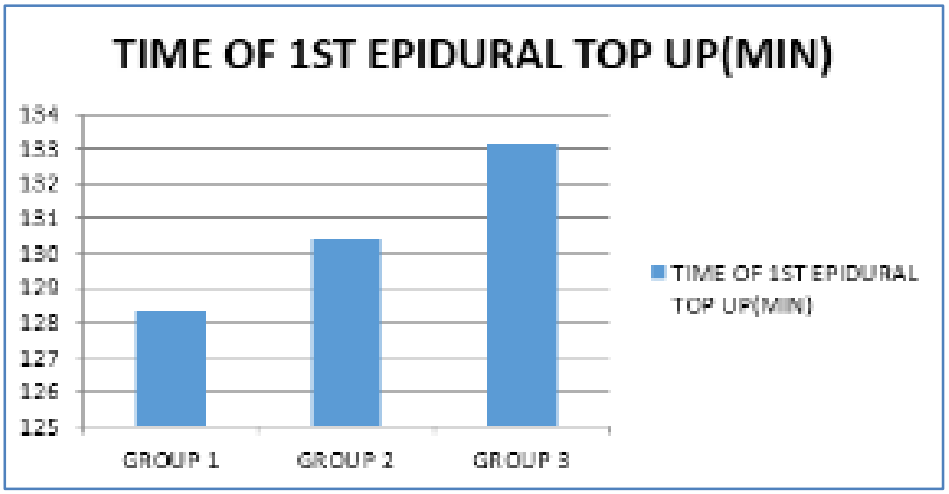
The time taken for 2 segment regression denotes the duration of action of the drug. It was highest in Group 3 (Bupivacaine+Clonidine), followed by Group 1(Bupivacaine+Normal saline) and Group 2 (Bupivacaine+$MgSO_4$) with values 122.37±8.028 min, 115.80+9.197 mins 113.40+5.11 mins respectively ($p < 0.05$). (Graph 5).



Graph 5: Time of 2 segment regression

The time for first top up was longest in Group 3 (Bupivacaine+Clonidine) followed by Group 2 (Bupivacaine+$MgSO_4$) and Group 1 (Bupivacaine+Normal Saline) at 133.57±7.520 mins, 130.43±9.804 mins and 128.33±6.493 mins respectively ($p<0.05$). (Graph 6)



Graph 6: Time of first epidural top up

The range of heart rate (HR) in Group 1 is from 74.30 to 91.30 beats per min. In Group 2 the variability is from 76.7 to 87.97 beats per min. In Group 3 it is from 73.07 to 83.71 beats per min. At 20 min there was a decrease in HR compared to baseline in all the three groups, more in Group 3 than other two groups. There is no significant change in HR in between the groups and within the group's up to 20 min. From 25 min onwards there is difference in the HR in between the three groups with p value <0.05. This shows that it is statistically significant. (Graph 7)

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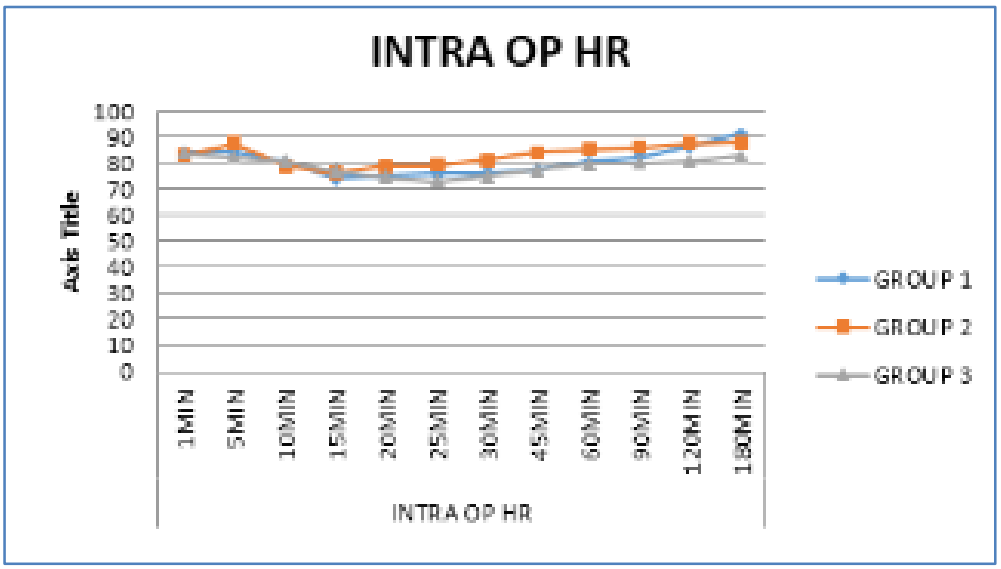
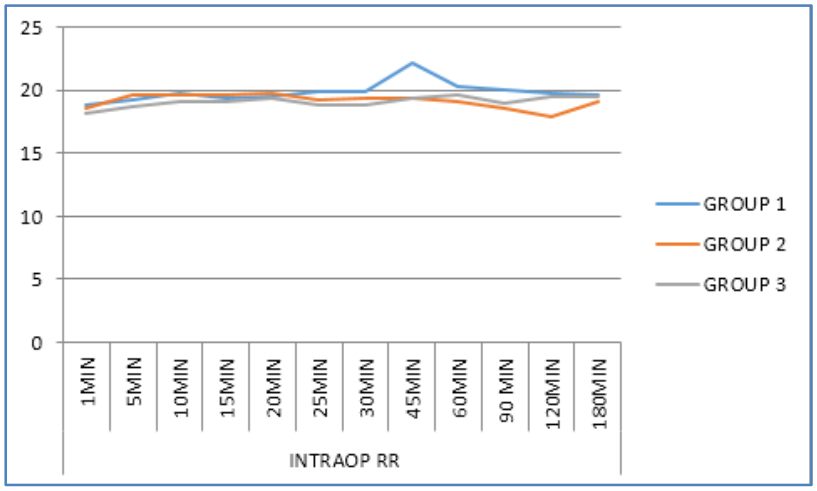


Graph 7: Intra operative Heart Rate

The range of respiratory rate (RR) in Group 1 was (18.83±2.866 to 22.23±11.85 breaths per min); Group 2 (17.93±2.100 to 19.83±3.041breaths per min); and in Group 3 (18.67±2.591 to 19.57±2.528 breaths per min).There is no significant variation in Respiratory rate in between the groups (p<005). (Graph 8)



Graph 8: Intra op Respiratory Rate

The systolic blood pressure ranged from 100.67±11.146 to117.87±8.807; 107.20±12.541 to 119.53±9.247; 90.17±18.562 to 119.97±7.726mm of Hg in Groups 1, 2 and 3 respectively. There was decrease in SBP when compared to base line SBP at 20 min. The variation in Systolic blood pressure between the groups and within the groups is significant (p< 0.05) from 20 min onwards. The change is more in Group 3 (Bupivacaine+Clonidine) is more than Group 2(Bupivacine+$MgSO_4$) and Group 1(Bupivacaine+Normal Saline). (Graph 9)

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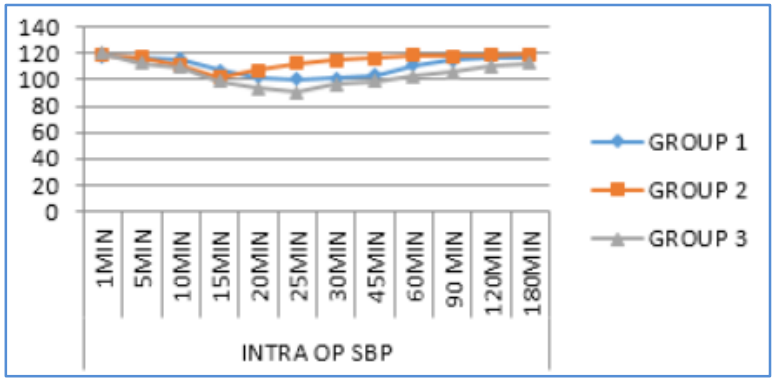
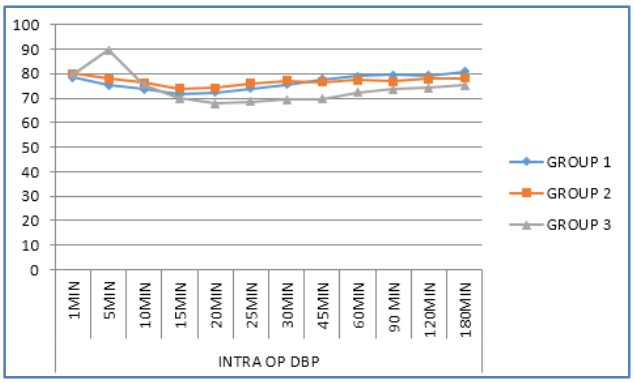


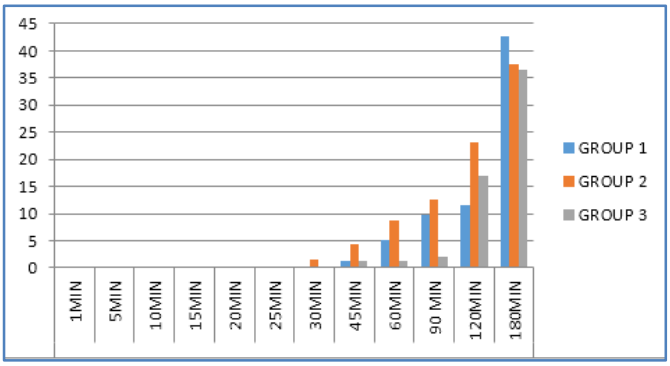
Graph 9: Intra op Systolic Blood Pressure

The range of Diastolic blood pressure in group 1 is from 71.40±6.262 to 80.77±6.202 mm of Hg, in Group 2 it is from 73.90±6.530 to 79.93±6.664mm of Hg, in Group 3 it is from 67.67±6.865 to 89.77±7.150mm of Hg. The difference in Diastolic blood pressure is statistically significant ($p < 0.05$) from 20 min onwards. (Graph 10)



Graph 10: Intra op Diastolic Blood

The Visual analog score (0–100) in Group 1 is from 1.40±5.334 to 42.77±11.097, in Group 2 1.47±5.582 to 37.43±13.617, in Group 3 it is from 1.33±5.074 to 36.60±10.318.The VAS score did not vary significantly in between the Groups upto 45 min ($p<0.05$). (Graph 11)



Graph 11: VAS Score Pressure

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Sedation is observed in 30% of the patients in Group 3 (Bupivacaine+Clonidine) compared to nil patients in Group 2(Bupivacaine+MgS4) and Group 1(Bupivacaine+Normal Saline). Clonidine group patients were calm and drowsy but arousable. This finding was quite significant ($p<0.01$). Addition of Clonidine did not affect post spinal shivering as 34% patients in clonidine group and 25% of patients in control group complained of shivering which found to be statistically significant (p value <0.01).

Nausea and vomiting were noticed in 10 % of control group, 7% of $MgSO_4$ Group and 10 % in Clonidine Group which was not found to be statistically significant (Table 1).

Variable	Group 1	Group 2	Group 3	Sig
Sedation	0	0	9(30%)	0.000
Shivering	7(25%)	0	10(34%)	0.000
Nausea and vomiting	3(10%)	2(7%)	3(10%)	0.127

Table 1: Adverse Effects

DISCUSSION: Post-operative pain may produce a range of detrimental effects which if untreated may progress to chronic surgical pain. Epidural anaesthesia and analgesia, gives a greater flexibility with control over haemodynamics and minimal perioperative physiological derangements. However, titrating various drug combinations may reduce the side effects; optimize the onset of action and duration for the patients comfort. Many adjuvants are in use like opioids, α2 agonists, cations (Mg^{2+}) which can improve the performance of anaesthetic agents.

We have chosen epidural Magnesiun sulphate and clonidine for their effects on anaesthesia and analgesia produced by epidural bupivacaine.[4-6]

The demographic parameters were compared and there was no significant variation between the groups (p value >0.05). The mean age was 36.33±13.24 yrs, 41.30±13.75 yrs and 34.13±12.74 yrs in Group 1, Group 2, Group 3 respectively. There is also no variation in mean height (167.17±9.13 cms, 164.03±8.61cms, 164.47±9.35cms in Group 1, 2, 3 respectively) and weight (62±10.3 kgs, 62.2±8.4kgs, 61.83±11.2 kgs in Group 1, 2, 3 respectively) among the groups. There is no significant gender variability as 66.7% were males and 33.3% were females in all the three groups.

The time taken to achieve sensory blockade at T6 level was lower in group 2 where Magnesium sulphate was added to bupivacaine (14.0±2.1 min), followed by Group 3 (Bupivacane+Clonidine) with 18.0±2.6min and was slowest in Group 1 with 20.1±2.9 min. This finding was statistically significant.

Noxious stimulation leads to the release of neurotransmitters, which bind to various subclasses of excitatory amino acid receptors, including NMDA receptors. NMDA receptor signaling may be important in determining the duration of acute pain. Therefore, NMDA receptor antagonists may play a role in the prevention and treatment of post-injury pain. Magnesium blocks calcium influx and non-competitively antagonizes NMDA receptor channels. Mg can have an effect on pain when used alone, but it has also been shown that it can reveal the analgesic properties of opioids.

Ghataket al[3] in their study showed similar findings the time taken to achieve a sensory level of T6 was lowest for and magnesium sulphate Group (11.08 min) followed by and clonidine Group (16.93 min) as compared to plain Bupivacaine Group (18.73 min) which was statistically significant

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(p<0.001).Farouk[7] in his study concluded that addition of magnesiun sulphate to bupivacine acts as preemptive analgesic.

Syal et al[8] in their study comparing the time of onset for epidural Bupivacaine (10 ml of 0.125%) with epidural Bupicacaine and Clonidine (60 µg) for epidural analgesia for labour found that onset of analgesia was faster by addition of clonidine (statistically significant). While Hansen et al[9] noted that analgesic effect of clonidine 2µg/kg as an adjuvant to caudal block with Bupivacaine 0.25%; 0.5ml/kg was similar when administered IV or caudally.

Chassard et al[10] in their study for labour analgesia with sufentanyl and 0.0625% Bupivacine with addition of clonidine (100 and 150 µg) did not find any difference in time of onset of analgesia.

The time for 2 segment regression which in fact denotes the duration of action of drug was significantly higher in Group 3 (122.37 min) followed by Group 2 (115.80min) as compared to plain bupivacaine(113.40 min). This finding was statistically significant (p<0.05).

Clonidine is a selective partial α2 adrenergic agonist with a selectivity ratio of 200: 1 in favor of alpha 2 receptors. It is lipid soluble and easily penetrated BBB to reach the hypothalamus and medulla when injected epidurally. It stimulates inhibition alpha-2 adrenoreceptors to reduce central neural transmission in the spinal neurons. Inhibition of substance –p release is also believes to be involved in analgesic effect. Cholinergic mechanism may also be involved, at least in part, in analgesia due to neuraxially administered clonidine.

The alpha -2 adrenoreceptors are located on the afferent terminals of both peripheral and spinal neurons, on neurons in the superficial laminae of spinal cord and within several brainstem nuclei. The superficial laminae of dorsal horn contains 3 groups of neurons: tonic, adapting and single spike firing; all of which are important neuronal structures for pain transmission, receiving most of their primary sensory input from A delta and C fibres. The analgesic effect of clonidine is more potent after neuraxial administration indicating a spinal site of action and favorsneuraxial administration.

Sedation is due to its action on locus ceruleus. Sedation after epidural clonidine is due to its systemic absorption and vascular redistribution to higher centres. Clonidine causes decrease in peripheral resistence, renal vascular resistence, heart rate and blood pressure. Clonidine alone does not produce profound respiratory depression even after massive overdose nor does it potentiate respiratory depression from opioids.

Tripi et al[11] in their double blind prospective study on children undergoing ureteroneocystostomy concluded that addition of clonidine to bupivacaine significantly increase the duration of caudal analgesia.Akin et al[12] concluded that caudal clonidine prolongs the duration of analgesia produced by caudal levobupivacaine without causing significant side effects.

Chassard et al[10] in their study found that mean duration of anaesthesia significantly (p<0.01) higher with addition of clonidine (100 µg and 150µg; 130 and 144 min respectively) as compared to Sufentanyl and 0.0625% Bupivacaine alone (105 min).They further noticed that the percentage of patients not asking for additional analgesia was greater in the group with addition of clonidine. Ghataket al[3] in their study noticed that 2 segment regression though was more in clonidine group (145.33 ± 27.74 mn) as compared to magnesium group (130.33 ± 33.94 min) and control (123.00 ± 28.08min) was not statistically significant. They further noted that the time for first epidural top up was maximum for clonidine group (180.33 ± 29.97), followed by magnesium group.

Yousef and Amr[13] and Bhanwait et al[14] in their study evaluating the effect of single epidural bolus of Magnesium to Fentanyl in patients with combined spinal epidural anaesthesia found that

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mean duration of analgesia was significantly longer with addition of Magnesium sulphate (340±28.8 min) as compared to fentanyl alone (164±17.1 min) (p value<0.01). The frequency of rescue analgesic was also significantly less on addition of magnesium sulphate (p <0.01) Albrecht et al[15] in their review found that the time for first analgesic request increased by 11.1% after intrathecal magnesium administration and by 72.2 % after epidural administration with doses between 50 and 100 mgs.

Bahrenberg et al[16] from their experimental study in adult dogs concluded that epidural $MgSO_4$ produced antinociceptive effect of similar magnitude as produced by epidural morphine without causing any motor deficits. No potentiation of morphine antinociception was however observed. DeRossi et al[17] in their experimental studies on adult sheep that addition of magnesium sulphate to lumbosacral epidural ketamine doubled the duration of analgesia as compared to epidural ketamine alone.

There is a decrease in heart rate in all the groups after 20 min and more significantly in group 3 (clonidine+bupivacaine). This is due to the action of clonidine which has the property of decreasing the heart rate. Blood pressure also decreases as compared to base line in all the groups from 20 min onwards and that too more in group 3, also due to the action of clonidine.

The changes in magnesium sulphate group with respect to clonidine group and control group is not much significant, hence haemodynamically stable as compared to clonidine.

There was no change in respiratory rate intra operatively in clonidine group and Magnesium group as compared to control group showing that at that dose there is no respiratory depression.

Sedation was seen in clonidine group and there was significant change in VAS scores in between the groups after 45 min. The clonidine group had a decrease in VAS scores compared to magnesium group and control group owing to its long duration of action and sedation.

Eisenach et al[18] showed a reduction in heart rate by upto 20% and drop in arterial blood pressure by 18% with use of 160 micrograms of clonidine. Hussien[19] noted that clonidine decreased both mean arterial blood pressure and heat rates. However, this finding was not noticed in patients who received epidural magnesium sulphate. Chassard et al,[10] found that the mean arterial pressures decreased significantly in clonidine group, more rapidly with 160 micrograms as compared to 100 micrograms. The fall in pressures was more significant after 20 mins. They did not observe any significant changes in heart rates.

Farouk et al[7]&Ghatak et al[3] did not find any significant hemodynamic and respiratory changes with epidural magnesium. However, they did have these changes with clonidine. Kara et al[20] noticed hypotension when magnesium was given intravenously. Ghataket al[3] found that VAS scores varied in all three groups significantly at the end of 45 mins.

Nausea and vomiting was noticed in 3 (10%), 2 (7%) and (10%) of patients in group 1, 2 and 3 respectively showing no statistical significance. Sedation was seen in clonidine group in about 30% of patients compared to no sedation in bupivacaine group and magnesium sulphate groups which was statistically significant. Shivering was seen in bupivacaine group and clonidine group but not in magnesium sulphate group. Clonidine does not appear to reduce post spinal shivering.

CONCLUSION: The use of adjuvants in epidural anaesthesia gives a scope to improve the quality of anaesthesia with minimal or nil adverse effects. The results of present study comparing the effect of magnesium sulphate and clonidine as adjuvants to epidural bupivacaine, are comparable with respect to time of onset of sensory blockade, duration of anaesthesia and any adverse effects, suggest

that by co administration of magnesium sulphate (50 mg), there is predictable rapid onset of nerve blockade without any side effects and clonidine (150 micrograms) produces prolonged duration of anaesthesia with sedation.

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DOI: 10.14260/jemds/2015/1359

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FINANCIAL OR OTHER COMPETING INTERESTS: None

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Date of Submission: 11/06/2015.
Date of Peer Review: 12/06/2015.
Date of Acceptance: 29/06/2015.
Date of Publishing: 03/07/2015.