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Comparative Study of Analgesic Effect of Epidural Clonidine and Magnesium Sulfate as an Adjuvent to Bupivacaine in Orthopaedic Lower Limb Surgeries

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ABSTRACT

BACKGROUND: This prospective double blind, randomized controlled trial study was undertaken to compare the onset and duration of analgesia with the epidural bupivacaine and its combination with either magnesium sulphate or clonidine, to establish the ideal combination of drug with least side effects.

MATERIAL & METHODS: The study included 90 patients between age group 20-60 yrs. of ASA grade I & II, scheduled for orthopaedic lower limb surgery. Patient were randomly assigned to three groups of 30 patients each. Gr. I- 20 ml of 0.5% bupivacaine + 5ml of NS, Gr.II- 20ml of 0.5% bupivacaine + 50 mg magnesium sulphate + 4ml of NS and Gr. III- 2 ml of 0.5% bupivacaine + 50 mic.g clonidine + 4 ml of NS. The time of injection, onset of analgesia, level of sensory and motor block, hemodynamic changes and side effects were recorded.

RESULTS: The time of onset of sensory analgesia is least with clonidine, the time of regression of sensory analgesia to L1 segment is maximum with clonidine, time for onset of motor block is least in clonidine group, the grade of motor block is maximum in clonidine group, hemodynamic effects and side effects were not significant.

CONCLUSION: we conlcuded that we have quicker time of onset of sensory and motor blockade, greater duration of analgesia, with no significant increase in side effects with clonidine group than the magnesium sulphate group.

KEYWORDS : Epidural anaesthesia, Bupivacaine, Clonidine, Magnesium Sulfate, Lower limb surgery.

INTRODUCTION:

Pain has been defined by International Association for study of pain as " an unpleasant sensory and emotional experience associated with actual or potential tissue damage". Pain relief has been carried out by a variety of techniques like administration of local and systemic analgesic, cryoanalgesia, electric stimulation and acupuncture. Each of these techniques has their own advantages and disadvantages.

Regional anaesthesia is the most frequently used anaesthesia for orthopaedic lower limb surgeries. Epidural anaesthesia offers advantages, which are difficult to duplicate with general anaesthesia. It induces less physiological disturbances than spinal anaesthesia, has low incidence of neurological sequel and postdural puncture headache although onset of action is much slower (10-20 min) than spinal blockade.[1-2]

Epidural analgesia was introduced by Siccard and Cathelin in 1901.[3] Epidural technique can be used as a single shot technique or with a catheter that allows intermittent boluses and / or continuous infusion. The epidural agent is chosen based on the desired clinical effect. The quality of the epidural anaesthesia has been reported to be improved by the addition of opioids and other drugs such as clonidine[4], dexmedetomidine, magnesium sulphate[5], neostigmine, ketamine and midazolam , but no drug to inhibit nociception is without associated adverse effects.

Clonidine hydrochloride is an imidazole derivatives with alpha-2 adrenergic agonistic activity. The intrinsic analgesic effect of clonidine has been demonstrated with a large dose of clonidine alone given intrathecally or epidurally to control both intraoperative and postoperative pain. Epidural clonidine improves the quality of anaesthesia, reduces the doses requirement of the anaesthetic agent and provides a more stable cardiovascular course during anaesthesia with fewer side effects.[6]

Magnesium is the fourth most plentiful cations in the body. It has antinociceptive effects in animal and human models of pain. It has been reported that intrathecal or epidural magnesium enhances opioid antinociceptive in an acute incisional model. These effects have prompted the investigation of magnesium as a postoperative analgesic.[7]

This study was conducted to evaluate the effect of epidural administration of bupivacaine alone, bupivacaine with clonidine, bupivacaine with magnesium on duration af analgesia and first pain complain by patient and to establish the ideal combination of drug for epidural anaesthesia with least side effects.

MATERIALS AND METHODS:

This study was carried out in patients undergoing orthopaedics lower limb surgeries in Department of Anaesthesia , NIMS Medical College and Superspeciality Hospital, Jaipur after obtaining institutional ethical committee approval and written informed consent. Total 90 patients undergoing elective orthopaedics lower limb surgeries aged 20 – 60 yrs of either sex, belonging to ASA physical status I & II were included in this prospective randomized, double blind study. Patient with a history of diabetes mellitus, hypo or hypertension, respiratory disease, epilepsy, cardiac disease, spinal injuries, spinal defects, pt on beta blockers,antidepressant, psychiatric patient, deaf &dumb patient were excluded from the study.

Pre-anaesthetic checkup was done a day before, which included complete history of patient, general physical and systemic examination

of lumbosacral region, any cardiac or pulmonary pathology of significant nature. Pulse rate , blood pressure, respiratory rate were noted.

Routine investigation included- Hb, TLC, DLC, BT, CT, Chest PA view, ECG, Blood urea, serum creatinine, SGOT, SGPT, SGPT, fasting and random blood sugar.

A written informed consent was taken from patient for epidural block & drug which were . used. Proedure was explained to the patient.

Patient received no premedication and upon arrival of patient into the operating room, ECG, pulse oximetry(spo_2) and noninvasive blood pressure(NIBP) were monitored. All patient were preloaded with 500ml of ringer's lactate solution. Epidural block was performed with 18G Tuohy needle at the L3- L4 or L4-L5 interspace in the sitting position after back of patient painted with povidine iodine.

The patients were randomly divided into three groups:

Group-I were injected isobaric bupivacaine 0.5% (20ml) with 5ml normal saline 0.9% (NS)

Group-II were injected isobaric bupivacaine 0.5%(20ml) with 50 mg magnesium sulphate(diluted in 1ml NS) with 4ml o.9%NS.

Group-III were injected isobaric bupivacaine0.5%(20ml) with 50 mic.g clonidine(diluted in 1ml NS) with 4ml 0.9%NS.

After confirming the position of the Tuohy needle , total dose of the desired solution was given slowly. Patients were injected according to the random assignment, then patients were placed in supine position with a pillow under their shoulders. No head down tilt was given.The time of injection, onset of analgesia, level of sensory & motr block were noted. Sensory blocked was examined by pinprick method on abdomen,perineum & lower limb by 25G disposable needle. The onset and level of sensory blockade were noted. Motor blockade was noted by using modified Bromage criteria.

Intraoperative pulse, blood pressure, SPO2, sedation and side effects were monitored every 5 miutes for first 30 minutes followed by every 10 minutes upto completion of surgery. Postoperatively pulse, blood pressure, SPO2, VAS score(<4= satisfactory pain relief and >4= analgesic supplement) and side effect were monitored.The parameters were noted at 30 minutes and then at1,2,4,8,12 hrs upto 1st dose requirement of analgesic by patient (VAS score >4).

Following side effects were looked for- hypotension(systolic pressure <90 mmHg or 30% decrease from baseline), hypertension(SP.>160 mm or >100mmHg), bradycardia(pulse rate< 60 bpm), respiratory depression(SPO2< 90%), sedation, headache, nausea & vomiting, shivering, pruritis.

Motor blockade was assessed by using modified Bromage scale(0- no paralysis, 1-inability to raise the extended knee, 2- inability to flex the knee, 3- inability to flex the ankle joint).[8] Sedation was assessed on a four point scale (0- awake and alert, 1- mildly sedated and easily aroused, 2- moderately sedated and aroused by shaking, 3- deeply sedated anddifficult to be aroused by physical stimulation.

Pain was assessed by Visual Analogue Scale[9](0- no pain, 1,2,3- mild pain, 4,5,6- moderate pain, 7,8,9- severe pain and 10- worst imaginable pain).

Time to two segment regression to first epidural top up requirement were recorded.

All the data was analysed statistically using unpaired t- test and conclusion were drawn.

RESULTS:

There were no differences in age, height, body weight, body mass index(BMI) between the groups. These groups were similar in the maximal dermatome achieved. No difference in the quality of sensory and motor block befor and during the surgery was noted between groups. Systolic , diastolic arterial blood pressures, heart rates and oxygen saturations remained stable, and there was no significant difference between the groups.[Table 1]

The time of onset of sensory analgesia is least with clonidine group(13.67+/-2.54 minutes) followed by magnesium sulphate group(17.33+/-2.86 minutes) and maximum in bupivacaine group(18.67+/- 2.54 minutes). The difference is significant in clonidine group. The difference between the groups was statistically not significant($p>0.05$) between group 1&2 and significant ($p<0.05$) between group 1&3 and 2&3.[Table 2]

The time of regression of sensory analgesia to L1 segment is maximum with clonidine group(218+/-20.74 minutes) followed by magnesium sulphate group(196.9+/-10.95 minutes) and least with bupivacaine group(148+/-24.83 minutes). The difference between the groups was statistically significant($p<0.05$).

The time of onset of motor block is least in clonidine group(20.31+/-5.65 minutes), followed by magnesium group(28.2+/-3.95 minutes), and maximum in bupivacaine group (33.21+/-3.75 minutes). The difference among groups were highly significant ($p< 0.05$). [Table 3]

The grade of motor block is maximum in clonidine group, followed by magnesium group and minimum in bupivacine group. The difference was not significant($p>0.05$) between group 1&2 where as it was significant ($p<0.05$) between group 1&3 and 2&3.

Hemodynamic effects are not significant as the effect on pulse rate in all three is not significant both intraoperatively and postoperatively. While intraoperatively fewer patient in clonidine group had hypotension and require medication, but not in the other two groups. Postoperatively significant difference was not there between the three groups regarding incidence of hypotension..

The incidence of other side effects like respiratory depression, pruritis, nausea and vomiting, sedation, shivering, headache etc. is not increased in all the three groups.

The mean duration of analgesia is significantly prolonged in clonidine group(500+/-22.74 minutes), followed by magnesium sulphate group (332+/-24.83 minutes) and least in bupivacaine group(290+/-28.77 minutes). The difference between the groups were highly significant($p<0.05$).[Table 4]

DISCUSSION:

The result of this study show that the addition of clonidine, centrally acting alpha 2 agonist results in quicker onset and maximum duration of analgesia with minimal acceptal side effects compared to magnesium sulphate and bupivacaine alone.

Earlier studies with 10-20 ml of 0.125% bupivacaine, reports suggest a quite unacceptably high failure rate and brief duration of action, despite the addition of adrenaline (Bleyart et al 1979). Hence in our study we used 0.5% bupivacaine. Besides this (Tunsletall and Ostheimer 1989) concluded that a single dose of bupvacaine upto 150 mg may be given and doses upto 50mg two hourly may be added subsequently.

Scott D, Mc Clure J, Giasi R et al 1980 concluded that increase in the concenteration of epidural bupivacaine in surgical patients from 0.5% to 0.75% with a concomitant increase in dosage from approximately 100 to 150 mg produced more rapid onset and prolong sensory anaesthesia , a greater frequency of satisfactory sensory anaesthesia and more profound motor blockade. So in our study by usng higher concenteration and greater volume, we masktwo major epidural drawback i.e late onset of analgesia and less motor blockade.

Rucci et al. Showed that the time to onset to sensory block in L1 was 11+/-3 minutes in group of patients receiving a total of 20 ml 0.5% bupivacaine, our study shows onset to L1 level was 18.67 +/- 2.54 minutes in control group and 13.67+/- 2.54 with clonidine group.

Clonidine induces dose dependent spinal cord antinociception, mainly through stimulation of alpha2- adrenoceptors in the dorsal horn, mimicking the activaton of descending inhibitory pathways.[10] Motor and sensory blockade of local anaesthetics are enhanced by

clonidine. The effects of clonidine on the prolongation of nerve blockade are clearly dose dependent. We also found in our sudy that time for regression of sensory analgesia to L1 segment was 148 highest in clonidine group (218+/- 20.74 minutes) followed by magnesium group (196.9 +/- 10.95 minutes) and it was 148+/- 24.83 minutes in control group of pateient.

The mean time of total duration of analgesia in our study of the three groups and their p value shows significant differences between three groups. The maximum duration of analgesia upto VAS>4 is in clonidine group, followed by magnesium sulphate group and least in bupivacaine alone group. By comparing with the other similar studies(Reynolds et al 1989, Strebel s et al 2004 and Arcioni R et al 2008)[5] the result of our study is comparable statistically. These studies also shows significant prolongation in the mean duration of analgesia in clonidine and magnesium sulphate groups as compared to bupivacaine group.

Noxious stimulation leads to the release of neurotransmitters, which bind to various subclasses of excitatory amino acids receptors, including NMDA receptors . Activation of these receptors leads to calcium entry into the cell and initiates a series of central sensitization such as wind up and long term potentiaton in the spinal cord in the response of cells to prolonged stimuli.[11] NMDA receptor signalling may be important in determining the duration of pain.[12]Magnesium blocks calcium influx and noncompetitively antagonizes NMDA receptor channels.[13] Noncompetitive NMDA receptor antagonists can have an effect on pain when used alone.[14]

Hemodynamic effects were not significant as the effect on pulse rate on all three group were not significant both intraoperatively ond postoperatively.[15] While intraoperatively fewer patient in clonidine group had hypotension required medication, but not in the other two groups. [16] Postoperatively significant difference was not there between the three groups regarding incidence of hypotension. Comparison with other studies (Rucci et al 1985, Michael J. Paech et al 1997 and A. Bilir et al 2007) also showed almost similar incidence of hypotension.[17]

The incidence of other side effects like respiratory depression, pruritis, nausea and vomiting, sedation[18], shivering[19], headache etc. were not increased in all three groups. Our results are comparable with other studies of Rucci et al 1985, Klimscha et al 1995, Michael J. Paech 1997 and A. Bilir et al 2007.[20]

CONCLUSIONS:

After comparing the results of the three groups, we see that by addition of magnesium sulphate and clonidine to the bupivacaine in epidural anaesthesia, we have quicker time to onset of sensory and motor blockade, greater duration of analgesia, with no significant increase in side effects. The effects are more pronounced with clonidine group than the magnesium sulphate group.

Thus clonidine 50 mic.g. along with 20ml of 0.5% bupivacaine can be recommended in adult patient between agr of 20-60 yrs, with ASA grade I &II, in orthopaedic lower limb surgeries with analgesia extending into the post operative period. It is found to be an ideal and reliable combination for quicker onset and maximum duration and maximum duration of analgesia wit minimal acceptal side effects, compared to 50 mg of magnesium sulphate and bupivacaine alone.

However, the optimum drug & dose combinations needed for maximum safe results perhaps demand more study on a large scale so that more individualization can be achieved and the quality of anaesthesia improved further.

Table No. 1 Patients characteristics and baseline clinical variables:

Variables	Group 1	Group2	Group3
AGE (Yrs)	32.36+/- 7.30	30.2+/- 10.7	30.4 +/- 9.18
SEX M:F	28: 2	27 : 3	25 : 5
Baseline HR	84.8 +/- 6.38	86.73 +/- 8.54	83.13 +/- 7.38
Baseline Systolic BP	119 +/- 6.67	121 +/- 7.11	125.07 +/- 6.98
Baseline Diastolic BP	78.13 +/- 4.89	79.93 +/- 4.71	80.6 +/- 6.37

Table No. 2 The mean time of onset of sensory analgesia in three groups:

Group	Mean+/- S.D
Group1	18.67 +/- 2.54
Group2	17.33 +/-2.86
Group3	13.67 +/-2.54

Table No. 3 The mean time of onset of motor block:

Group	Mean +/- S.D.
Group1	33.21 +/- 3.75
Group2	28.2 +/- 3.95
Group3	20.31 +/- 5.65

Table No. 4 The mean time for total duration of analgesia in three group:

Group	Mean +/- S.D.
Group1	290 +/- 28.77
Group2	332 +/- 24.83
Group3	500 +/- 22.74

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