ORIGINAL RESEARCH PAPER

Anesthesiology

KEY WORDS:

COMPARATIVE EVALUATION OF ADDITION OF CLONIDINE VS NORMAL SALINE TO THE PHARMACODYNAMICS AND PHARMACOKINETICS OF INTRATHECALLY ADMINISTERED HYPERBARIC BUPIVACAINE FOR SPINAL ANAESTHESIA IN LOWER LIMB ORTHOPAEDIC SURGERIES

Dr.Anuradha Swaminathan Prof. M.D., D.A. Madras Medical College

ABSTRACT

INTRODUCTION: This study was undertaken to assess the behaviour of intrathecal clonidine as an adjuvant to bupivacaine in augmenting sensory block in patients undergoing lower limb surgeries.
MATERIALS AND METHODS: Patients were randomly divided into two groups of 30 each. Group N: 16.25 mg of 0.5% hyperbaric bupivacaine + 0.25 ml of normal saline, Group C: 16.25 mg of 0.5% hyperbaric bupivacaine + 0.25 ml(37.5mcg) of clonidine. Onset and duration of sensory block and motor block, the highest level of sensory blockade, duration of analgesia and side effects were assessed.
RESULTS: The onset of motor block was faster in group C when compared to group N. The time to reach Bromage scale 3 was fastest in group C. The duration of sensory, motor blockade and duration of analgesia was longer in group C than group N. The time to regression time to S1 was longer in group C. Duration of analgesia was significantly prolonged in group C.
CONCLUSION: Supplementation of bupivacaine spinal block with low dose of intrathecal clonidine(37.5mcg) produces a significantly shorter onset of motor and sensory block and a significantly longer sensory and motor block than bupivacaine with normal saline

INTRODUCTION

Spinal anaesthesia is a well known technique for lower limb orthopaedic procedures. It is easy to perform and provides faster onset and effective sensory and motor block. Bupivacaine produces long lasting spinal anaesthesia which is useful in orthopaedic procedures without TNS. Recently there has been an interest in using analgesic additives to intrathecal local anaesthetics to decrease the dose of LA and maintaining or improving anaesthetic success and also providing effective postoperative analgesia. Various studies had been conducted to evaluate the efficacy of addition of clonidine to hyperbaric bupivacaine. The a2 adrenergic agonist clonidine has a variety of different actions including the ability to potentiate the effects of LA. However unlike spinal opioids, clonidine does not produce pruritus and respiratory depression. It also prolongs the sensory blockade and reduces the requirement of postoperative analgesics. This study was designed to evaluate the efficacy and adverse effects of small dose clonidine (37.5 g) added to 0.5 % hyperbaric bupivacaine administered intrathecally in patients undergoing elective orthopaedic lower limb surgeries.

AIM OF THE STUDY

To compare the effect of addition of clonidine Vs normal saline to 0.5% hyperbaric Bupivacaine administered intrathecally for lower limb orthopaedic surgery with respect to

- Time to onset of sensory and motor block
- Duration of sensory and motor block
- Quality of intraoperative anaesthesia
- Duration of effective postoperative analgesia
- Time for demand analgesia
- Side effects

MATERIALS AND METHODS

The study was conducted at the Government General Hospital, Madras medical College, Chennai-600 003 between april 2018-may 2018

Patients of ASA physical status 1 and 2 undergoing elective orthopedic lower limb surgeries.

This study was done after getting Rajiv Gandhi Government Hospital Ethical committee approval and written informed consent obtained from all the patients included in this study.

STUDY DESIGN

This study was a prospective double blinded randomized
Each group consisted of thirty patients assigned in a random manner:

Group C

Patients in this group received 3.25ml of 0.5% hyperbaric bupivacaine +37.5 µg(0.25ml) of preservative free Clonidine to a total volume of 3.5ml intrathecally.

Group N

Patients in this group received 3.25ml of 0.5% hyperbaric bupivacaine + 0.25ml of normal saline intrathecally. The final volume of injected solution was 3.5ml in both groups.

this study 0.5% hyperbaric bupivacaine in 8% dextrose manufactured by NEON, clonidine hydrochloride (CLONEON) 150 ug manufactured by NEON Labs Ltd, Thane and Normal saline HABEEB Pharmaceuticals.

Patients were prepared by the OT incharge anaesthesiologist under strict aseptic precautions, uninvolved in the administration of SAB or in the manufacture of drugs that were used in the study or in the observation of results.

The specific gravity of the injected solution is 1.025, 1.0211 in and N respectively. All the solutions were hyperbaric relative.

SELECTION OF CASES

Inclusion Criteria

- Patients in the age group of 18 to 60 undergoing elective orthopaedic surgery to lower limb
- ASA PS I and II
- Lower limb surgeries lasting less than 150 mts

Exclusion Criteria

- ASA PS III and IV
- Contra indications to SAB
- hypersensitivity to the study drug
- Renal or hepatic dysfunction
- Neurological diseases
- Bleeding diathesis

PRE ANAESTHETIC EVALUATION

Patients included in this study underwent thorough preoperative evaluation which included History, History of underlying medical illness, previous surgery, anaesthesia and hospitalization.

Physical examination

1) GC of the patient
2) Vital signs
3) Height and weight
4) Examination of CVS, RS, CNS and Vertebral columns
5) Airway assessment

Investigations
Hb, PCV, BT, CT ,RFT ,BLOOD SUGAR .ECG , CXR,Platelet count were done. Patients who satisfied the inclusion criteria were about the nature of the study and the anaesthetic procedure consent were obtained from all patients included in the study received Tab Alprazolam 0.5 mg 3Hrs before surgery All patients received in the premedication room pulse rate ,BP, RR, and Sp02 was noted. An IV line was secured with 16G cannula. Preloading done with RL. (500ml-1000 mi) over 20-30 minutes.

In the OT appropriate equipment for airway management and emergency drugs were kept ready Patient was shifted from the premedication room to OT. The horizontal position of the operating table was checked and the patient was placed on it. NIBP, SpO2, ECG leads were connected to the patient Preoperative base line systolic and diastolic BP, PR, SpO2 and RR were recorded. The anaesthesiologist who were unaware of the drug combination performed the SAB and made observations in all the patients involved in the study A midline puncture was performed using a 23G Quincke needle in sitting position. Then patient was placed in supine position. The time of intrathecal injection was considered as 0 and following parameters were

SENSORY BLOCK
Sensory block was assessed by loss of sensation to pinprick using 25G sterile needle. The assessment was started immediately after intrathecal injection and continued every 15sec till loss of pinprick sensation at 12 level. Onset of sensory block was taken as the time from intrathecal injection to loss of pinprick sensation at L2. At 20 mts interval after SAB the dermatomal level of sensory block was noted and this was considered as the maximum level of sensory block. Sensory block was checked every 15 mts till 2 segment regression from the maximum level of sensory block occurred. The level of sensory block at the end of surgery noted and there after assessment was carried out at 15 minutes interval till return of pinprick sensation to S2 dermatome. Duration of sensory block was taken as the time from SA injection to return of pin prick sensation to S2.

MOTOR BLOCK
Motor block was assessed using modified BROMAGE score
GRADE 1- Free movement of legs and feet
GRADE 2- Just able to flex knees with free movement of feet
GRADE 3- Unable to flex knees but with free movement of feet
GRADE 4- Unable to move legs and feet

Assessment of motor block was started immediately after the injection. It was tested every 15 seconds till BROMAGE GRADE of 1 was reached. Onset of motor block was taken as time to BROMAGE SCORE 1 from the time of SAB injection. The 20 mts of injection was noted and this was considered as the maximum degree of motor block. There after motor block regression was noted and duration of motor block was taken as time of motor block after from SA injection to return of BROMAGE score Vital signs and side effects. The systolic and diastolic BP, PR, RR and SpO2 were recorded every 1 minute for 5 minutes and then every 5 minutes throughout the intraoperative period. The above vital signs at the completion surgery were noted. Hypotension defined as fall in systolic BP >30 % from base line or MAP 60 mm of Hg. This was managed with Inj. Ephedrine 6 mg increments. Bradycardia was defined as heart rate 60/mt and this was managed with Inj. Atropine 0.01 mg /kg IV. Respiratory depression defined as RR <8/mt and or SpO2 < 85 % . This was planned to be managed with bag and mask ventilation or intubation and IPPV if necessary. Blood loss than the allowable loss was replaced with blood. The occurrence of reaction were assessed using Ramsay Sedation scale

Level 1: Anxious and agitated, or restless or both
Level 2: Co-operative, oriented and tranquil
Level 3: Responds to commands only
Level 4: Brisk response
Level 5: Sluggish response
Level 6: No response

Quality of surgical anaesthesia
SA was graded as excellent if there was no complaint of pain at any time during surgery. Good if there was minimal pain or discomfort which was relieved by a small dose of IV Pentazocine 0.5mg/kg and Poor if GA has to be administered.

Assessment in PACU
The patient was shifted to the PACU after completion of surgery the vital signs were recorded every 15mts in the 1st hour after surgery and at 30mts interval for next two hours and there after at hourly interval for the next 3 hours. Sensory and motor block assessment were done every till recovery of pin prick sensation to S2 and BROMAGE SCORE grade 1. Patients were shifted to postoperative ward after complete 15mts till resolution of motor blockade.

Assessment of pain and duration of analgesia:
In the PACU pain assessment using VAS were done every 15mts the end of surgery the degree of pain was assessed using VAS Scale score 4was reached. The VAS also noted whenever the Il VAS patient complained of pain and Inj. Diclofenac 75 mg IM was given. Duration of effective analgesia was defined as the time interval between onset of SAB and the time to reach VAS4 Patient were monitored for 24 hours to detect the occurrence of side effects like respiratory depression, nausea , vomiting and pruritus. Patients were also enquired about the occurrence of TNS which was Till described as pain/parasthesia in neck , buttocks legs or pain radiating to lower extremities after initial recovery from SAB involving within 72hrs.

Statistical analysis
The descriptive statistics of the variables studied as represented as two-way tables. The categorical factors are represented by the number and frequency (%) of cases. The continuous variables are represented by

Meassure of central tendency (like mean, median and mode) and Standard deviation (SD and range). The difference in the proportion are tested for significance using non parametric Chi-square test for variable measured on nominal scale. When testing for two factors the Mam-Whitney "U" or Wilcoxon two sample test (by Kruskal-Wallis 'H' test which is equivalent to chi-square) is used. For variables measured on a continuous scale, one way analysis of variance is employed.

OBSERVATION AND RESULTS
This study was conducted at the GOVT General Hospital Chennai. Sixty (60) patients were included in this double blinded randomized controlled study. The patients were divided into two groups. Patients in group N received 3.25 ml (16.25 mg) of 0.5% hyperbaric bupivacaine plus 0.25ml of normal saline. Patients in group C received 3.25ml (16.25mg) of 0.5% hyperbaric bupivacaine plus 0.25ml (37.5%) of Clonidine. Final volume of injected solution was 3.5ml in both groups.

DEMOGRAPHIC DATA
The two groups were comparable with respect to their age, height and weight. There was no statistically significant difference among two groups in demographic aspects.(Table No.1,2,3)

Duration of Surgery
The two groups were comparable with respect to the duration of surgery and there was no statistically significant difference among two groups in the duration of surgery.(Table No.4)

Onset of Sensory Block
The time taken to achieve a sensory level of L2 from the time of SAB was tested by pinprick. The mean time taken in group Nd 13.5 seconds and 122 103 seconds group C. There was statistically significant difference among two groups in the onset of was 125.33 ± sensory block. (Table No.5)

Types surgery in both groups
Both the groups were similar in the respect of ASA and types of surgeries (Table No.6)

Maximum level of Sensory Block
The range of maximum level of sensory block was T4-18 in both groups. The median of the of sensory block was T6 in both groups. There was no statistically significant difference among two groups in the maximum level of sensory block. (Table No.7)

Onset of Motor Block
The mean time taken to achieve grade-1 motor block in modified Bromage scale was 177.33 ± 10.80 sec ın group N, 173 674 21.73 sec in group C. There was no statistically significant difference among two groups in the Onset of Motor Block (Table No 8)

IM GRADE OF MOTOR BLOCK
m degree of motor block in both groups was grade 3. There tieally significant difference among two groups in the he maximum lximum grade of motor block
e No 9)

Duration of motor block
The mean duration of motor block was 190,31 39.32 min in group N 257.33 ± 37.95 in group C. There was statistically significant difference among two groups in Duration of motor block (P 0.0001) (Table No. 10)

Duration of sensory block
The mean time taken for return of pin prick sensation to S1 level was 217.67±39.60 min in group N 292.67 ± 38.163 min in group C . There was statistically significant difference among two groups in the Duration of sensory block (P 0.004) (Table No.11)

Time to two segment regression
The mean Time to two segment regression of sensory block was 206.5 ± 38.77 in group C. There was 150.17 ±4346 min in group N, significant difference among two groups in Time to two If regression (P 0.0001) (Table No.12)

Side effects and complications
Incidence of hypotension was 23.3% in group C and N. The incidence of bradycardia was 33.3% in group N. The group N. (Table No.16)

There was statistically significant difference in the incidence of bradycardia, hypotension and sedation. The incidence of other side effects was comparable among both the groups and it was of no statistical significant difference between the groups.

DISCUSSION
Subarachnoid Block is a commonly used anaesthetic technique for ursl. There has been a growing interest in the use of clonidine to spinal local anaesthetics. A2-agonist, like clonidine added to subarachnoid local anaesthetics have been shown to ide excellent surgical anaesthesia.

In this study 37.5µg of Clonidine was added to 16.25 mg (325 ml) of 0.5% Bupivacaine was studied in sixty (60) patients undergoing elective orthopedic lower limb surgeries. Onset of Sensory Block hyperbaric Bupivacaine and is efficacy as an adjuvant to the mean time to onset of sensory block was 125.33 seconds in group N, 122 seconds in group N. In our study, the addition of clonidine 37.5ug to hyperbaric Bupivacaine did not enhance the onset of sensory block. This correlated with the study done by Klimscha ct af., who intrathecally administered 0.5% Bupivacaine 5mg and 150µg clonidine and without Clonidine and observed that there was no significant difference between the two groups as regards to onset time of sensory block at T-11. T-11 dermotome level. Acalvoschi lurie et al., Statistically correlated merperidine alone 3.6+ 0.6min in his study found that there is no significant difference in the onset time for Clonidine 2ug/kg combined with Meperidine 1% 1mg per kg (3.9 ± 09min)

Maximum Level of Sensory Block
The median of the upper limit of sensory block was T-6 in group C and group N. There was no statistically significant difference among the two groups in the maximum level of sensory block. The addition of clonidine 37.5ug to hyperbaric Bupivacaine did not increase the spread of sensory level. Though studies conducted by Julia o Mc et al., 38 who found that addition of Clonidine 30µg to intrathecal 15mg higher for Clonidine than for control group. 0.5% Bupivacaine the sensory block to pinprick was De Kock et al., found in his study that addition of intrathecal doses (15ug, 45ug,75µg) with 5mg of Clonidine in increasing level of sensory block as the dose of Clonidine bupivacaine increased the increases

Onset of Motor Block
The mean time to achieve grade -1 on modified Bromage is 33seconds in group C, 173.61 seconds in group N The addition of clonidine 37,5 g to 0.5% Bupivacaine did not have any effect on the onset of motor block. This correlated with the study by Acalovsehi lurie et al., who at addition of Clonidine 2 g / kg with 1 mg/kg Meperidine 1% intrathecally had no significant difference compared to merperidine alone and merperidine combined with epinephrine 200ug in the onset of motor blockade

Maximum Grade of Motor Block
The median of maximum grade of motor block at the 30 minutes testing time measured using modified Bromage scale was grade-3 in two groups. There is no statistically significant difference among two groups. The clonidine induced intensity of motor block was correlated by Klimscha et al., showed that intrathecal Clonidine 150mcg added Lock study of Klimscha et al " and Bonnet et al., to 0.5% Bupivacaine significantly increased the intensity of motor block.

Bonnet et al., in his study the intensity in his study found that the intensity and duration of y was prolonged with increasing the dose of Clonidine from Bonnet et al., his motor block to 150ug added to 0.5% tetracaine.

Duration of Motor Block
In our study the mean duration of motor block was 81.903 in group N and 257.33 minutes in group C. The addition of Clonidine 37.5% Bupivacaine significantly prolonged the duration of motor block. The duration of motor block produced by subarachnoid hyperbaric Bupivacaine combined with Clonidine is shown to be base dependent. This correlated with the study by Wu CI et al., that increasing the dose of Clonidine during hyperbaric tetracaine spinal anaesthesia increased the duration of motor blockade (48%, 70%, 74%) respectively. in their study found that addition of 30ug of Juliao Mc et al 0.5% Bupivacaine (15mg) increased the clonidine to intrathecal De Negri et al in their study found that addition of Clonidine hyperbaric Bupivacaine 1% intrathecally prolonged the motor duration of motor blockade. 10Sug with blockade. Then correlated the study of Fogarty D et al., who concluded that of 75mcg of Clonidine with 2.75ml of 0.5% hyperbaric Bupivacaine prolonged the level by 216+97.1 minutes compared with control 138+59 9minutes time to two segment regression below LA regression of sensory block was significantly prolonged when Clonidine 150ug was added to 0.5% tetracaine compared with 0.5% tetracaine. L2 found in his study that addition of 3ue/kg of Clonidine of 0.5% Bupivacaine prolonged the two segment regression to 2 level compared with 0.5% Bupivacaine alone.

Duration of Sensory Block
The mean duration of sensory block (time to return of pin-prick at S-1) was 217.67 minutes in group N and, 292.67 minutes in C. There was significant difference among the two groups. The duration of sensory block was longest in group C. The addition of Clonidine 37.5µg to 0.5% Bupivacaine significantly prolonged the duration of sensory block in Clonidine group This correlated with the findings of Fogarty et alt who found that intrathecal Clonidine 75µg prolonged the effect of local anaesthetic 0 5% Bupivacaine 2.7ml in terms of spinal block Klimscha W et al" in their study found that Clonidine 150yg Combined with 0.5% 5mg Bupivacaine intrathecally prolonged the on of sensory block and two segment regression time Niemi L found in his study that addition of Clonidine 3g ky with 0.5% 15mg Bupivacaine spinal analgesia was prolonged by 217 his correlated with the study of Fogarty et at" who found that al Clonidine 75pg prolonged the duration of Bupivacaine 0.5% spinal block and the time to first analgesia (mean (2.75ml) spinal block and the t 2784

93.2minutes) Klimscha W et al2 in their study found that Clonidine 150mcg to 5mg of 0.5% Bupivacaine intrathecally prolonged spinal anaesthesia (267+23 minutes) Racle et al., in their study found that intrathecal Clonidine 1504g prolonged Bupivacaine spinal anaesthesia in elderly patients undergoing hip surgery and their technique was superior to the addition of adrenaline 200 ug to Bupivacaine. Juliao et al., in their study found that intrathecal 15mcg and 30mcg Clonidine combined with 15mg 0.5% Bupivacaine increased the duration of analgesia

Complications

The hypotension was dose dependent on Clonidine group. In our study the incidence of hypotension was 23.3% in group C , and 0.5% bupivacaine administered intrathecally, was correlated by study of Wu CI et al., who found that hypotension was more in 4Sug group compared with 15µg This incidence of hypotension was Group combined with 10mg tetracaine intrathecally 15mcg Filos Kriton et al in their study found that hypotension is the side effect This finding is in concurrence with the findings in our study. Fisenach James C st al in their study found that hypotension is observed with upper thoracic injection of low doses of lipid soluble drug Clonidine, where as no hypotension was observed with upper thoracic injection of large doses or after cervical or lumbar injection of any dose of Clonidine or after injection of poor lipid soluble Clonidine Decrease in blood pressure after thoracic intrathecal Clonidine injection is the result of a2 adrenoreceptor and muscarinic neuronal activation. Klimscha e al 2o in their found that intrathecal local anaesthetic decrease mean arterial pressure and sympathetic outflow by blocking axonal transmission along the spinal nerves. Therefore, one would expect the preganglionic sympathetic cellular inhibition by Clonidine would y dense axonal blockade by local anaesthetic, thus explaining Spinal thecal Clonidine does not decrease blood pressure more with large (g) Bupivacaine than with a small dose of 5mg. Incidence of bradycardia was 66.6% group N and 33.3 % in groupC. This correlated with the study by Filos Krtonly by vagomimetic effect. In our study three (3) patients in group N and one in up C had shivering. There was no statistical signficance among these. Clonidine actually reduces the post operative shivering after in the general anaesthesia. Pruritus, nausea, vomiting respiratory depression, urinary retention and transient neurological symptoms did not occur in any of the patients included in our study. Transient Neurological Symptoms (TNS) did not occur in any of our patients included in our study. Studies done by Freedman JM et al and Hampl KF et al., showed an increased occurrence of TNS in patients undergoing spinal anaesthesia with Lignocaine. According to their studies, spinal anaesthesia in the ambulatory setting and patients in any position during surgery contributed to TNS occurrence.

CONCLUSION

This study confirms the efficacy of 37.5mcg of Clonidine as a safe adjuvant to 0.5% hyperbaric Bupivacaine in subarachnoid orthopaedic surgeries. The addition of 37.5mcg of Clonidine to 3.25ml of 0.5% hyperbaric Bupivacaine provided excellent Surgical anaesthesia. Clonidine 37.5mcg added to 16.25 mg of 0.5%hyperbaric bupivacaine intrathecally prolonged postoperative analgesia and reduces the post operative analgesic requirements.

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