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Comparative Clinical Study Between Premixed and Sequential Administration of Intrathecal Clonidine With Hyperbaric Bupivacaine in Lower Limb Orthopedic Surgeries

KEYWORDS: Clonidine, Bupivacaine, Intrathecal

Jyoti Pushkar Deshpande	Poonam S. Ghodki	Shalini Sardesai
MBBS, MD (ANAESTHESIA), Assistant professor, Department of Anaesthesia , Shrimati Kashibai Navale Medical College ,Pune	MBBS, MD (ANAESTHESIA), Associate Professor, Dept.of Anaesthesia, Smt. Kashibai Navale Medical college, Pune.	MBBS, MD (ANAESTHESIA), Professor, Dept.of Anaesthesia, Smt. Kashibai Navale Medical college , Pune

ABSTRACT *Context: Clonidine alpha-2 agonist is used as adjuvant to intrathecal local anesthetic to improve intra-operative analgesia and to prolong sensory and motor block. We compared hyperbaric bupivacaine(HB) with intrathecal clonidine injected as premixed or in sequential manner.*

Aims: 1: To study sensory and motor block characteristics. 2: Postoperative analgesia. Settings and Design: Prospective randomized double blind study.

Methods and Materials: Sixty patients of either sex, age 18-65 years, ASA grade I or II undergoing lower limb orthopedic surgeries were randomly assigned to one of the following group of 30 each, using a slip in box technique:

Group M: Received mixture of 0.5% HB 15mg & Clonidine45ug.

Group S: Received 0.5% HB 15mg followed by Clonidine45ug in a separate syringe.

Statistical analysis: Two independent sample t- test used and p value ≤ 0.05 was statistically significant. Results: .Time to reach highest sensory level and highest bromage scale were less in group S when drugs administered sequentially. Prolonged duration of analgesia was seen in group S compared to group M.

Conclusions: Sequential technique hastens the onset of complete sensory and motor block, enhances the duration of sensory and motor block also the postoperative analgesia without much hemodynamic adverse effect.

Introduction: Subarachnoid block (SAB) is a commonly used safe & effective technique for producing anesthesia & early postoperative analgesia in a patient undergoing lower limb orthopedic surgeries. [1] Various adjuvants have been used along with bupivacaine for prolonging duration & improving quality of analgesia. Clonidine a selective partial α-2 agonist, is being demonstrated as a safe adjuvant to intrathecal local anesthetic & proven as potent analgesic & free of opioid related side effects.[1,2] Intrathecal clonidine not only improves the quality of anesthesia but also reduces perioperative anesthetic & analgesic requirement. [2,3,4] Number of factors affect the intrathecal spread & action of anesthetic solution, includes temperature , pH & density of solution, volume of the drug injected & height of the patient. We routinely mix adjuvants & hyperbaric bupivacaine (HB) in a single syringe before injecting intrathecally which may affect the density of both the drugs, hence their spread in cerebrospinal fluid (CSF) as well as action. [5,6,7] In view of few evidences of comparing premixed versus sequential administration of intrathecal clonidine with HB, we wish to conduct the study to investigate block characteristics, side effects & postoperative analgesia. Rational behind using two separate syringes for HB & clonidine administration is to minimize effect on density of both the drugs.

METHODS: After ethical committee approval & written informed consent, a double blind prospective randomized controlled trial was carried out on 60 American society of anesthesiologist (ASA) physical status I & II patients of either sex , aged 18- 65 years , weighing between 40-65kg, measuring more than 150cms in height undergoing lower limb orthopedic surgeries under SAB. Sample size was calculated using computer software (Epi Info). Patients with cardiovascular diseases, history of allergy to LA or clonidine, pregnant or lactating women, & those with condition that preclude spinal anesthesia were excluded from the study. The patients were randomly assigned using slip in box technique to receive the drugs either as a mixture(Group M) or sequentially(Group S). Group M received mixture of 3ml of 0.5% HB+45ug clonidine intrathecally, prepared in a single syringe & Group S received 3ml of 0.5%HB followed by 45ug clonidine through a separate syringe. The study drugs to be used were kept same throughout the study to avoid manufacturer's difference (HB &clonidine from Neon laboratories). All the patient were evaluated preoperatively & familiarized with visual analogue scale (VAS 0 =no pain&10=worst pain). Patients were fasted 6hrs & premedicated with oral alprazolam 0.25mg a night before. On arrival to operation theatre, standard monitors [pulse oximetry (SpO2), noninvasive blood pressure (NIBP) & electrocardiogram (ECG)], attached &baseline parameters were recorded. Intravenous (IV) access was established & patients preloaded with ringer lactate15ml/kg. Under all aseptic precautions lumbar puncture was performed in L3-L4 space with 26G Quincke needle via midline approach in sitting position. Drug was injected over 30sec (including the time for change of syringe in sequential group) & patient made supine. All the assessment was made by an independent anesthesiologist, who is blinded to both for anesthesia technique & anesthesia drug used for each patient. Hemodynamic variables were measured every2. 5 min for 15 min after SAB, then at 15 min interval for 1hr & then hourly for next 8hrs. Hypotension (systolic blood pressure below 90mmHg or fall below 30% of baseline) were treated with rapid infu-

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sion of IV fluid or inj. ephedrine IV 5mg as when needed. Bradycardia (heart rate less than50/min) treated with inj. Atropine 0.6mg IV. The onset & duration of sensory block was assessed by loss of pinprick sensation to 23G hypodermic needle on shin of tibia. Dermatomal level was tested every 2 min until stabilized & time to reach maximal block height was noted. Also the time of sensory regression by two segments from highest level was noted. The onset & duration of motor block was assessed initially, then every 5min for 29 min following SAB & then every 30 min till full recovery using modified Bromage criteria (0-no motor block, 1- inability to raise extended leg; able to move knees & feet, 2- inability to raise extended leg & move knee; able to move feet, 3-complete block of motor limb). Onset time was the time to first loss of motor power (i.e. grade 1). Duration of motor block was the time from onset to complete recovery. Sedation was scored using 4-point rating score after SAB intraoperatively & 2hr postoperatively (0- wide awake, 1-sleeping comfortably but responding to verbal commands, 2-deep sleep but arousable, 3-not arousable).

Duration of the surgery was noted. Postoperatively, pain score was recorded using VAS every 60 min till the VAS> 5 and rescue analgesia (injection diclofenac sodium (1.5mg/kg) in IV drip) was given & time was noted. All patients were observed for any side effect & complication. STATISTICAL ANALYSIS- The data was collected & comparison of variables between two groups and within each group with baseline values was done by using unpaired students t –test and paired t test respectively. Results were considered significant if p <0.05 & highly significant if <0.001. RESULT- Sixty patient fulfilling the inclusion criteria were randomly assigned to one of the two groups. The demographic data, total number, type &duration of surgical procedures were comparable in both groups (Table 1). The onset of sensory & motor block, maximal sensory block height was comparable in both groups (Table 2.) Time to achieve the highest sensory block & complete motor block was significantly less in sequential group S(sensory 5.2±2.18 min, motor 7.11±2.14 min) compared to mixed group M (sensory 6.4±2.21 min , motor 8.16±2.10min). The two segment sensory regression time was significantly prolonged, 211.48±24.76 minutes in group S as compared with 126.62±22.54 minutes in group M. Again the duration of motor block was significantly longer in group S (366.32±32.23min) than group M (269.28±36.23min). Duration of analgesia was also significant in group S (554.28±34.28) as compared to group M (356.32±32). Both groups showed fall in HR 6min after SAB with maximum fall at 45 min. We found fall in HR from baseline in 8 patients (26.67%) in group S compared to 4 (13.34%) in group M. Group M 2 & group S had 3 patients bradycardia. There was fall in mean arterial pressure(MAP) from baseline in 16.67% in group S & 13.24% in group M were comparable between the groups (table3).The maximum fall in MAP was at 45min & lasted for 8hrs. None of the patient had respiratory depression ,dry mouth, nausea, vomiting & headache postoperatively.

DISCUSSION: From our study it can be elicited that sequential technique provides early onset & prolongs the duration of analgesia without significant hemodynamic adverse effects. Clonidine a selective partial α-2 agonist has been proven to be of benefit for intrathecal use by increasing the duration & intensity of pain relief, also by decreasing the systemic & local inflammatory stress response.[8-11] Various studies have been carried out using intrathecal clonidine in the range of 15-150ug.But at higher doses (1-2ug/kg) side effects like marked sedation, hypotension & bradycardia are seen.[4] De kock et al., recommended a dose of 15-45ug of clonidine as optimal for spinal anesthesia.[12] Therefore, we studied 45 ug of intrathecal clonidine administered as premixed or sequentially with 3ml of HB.

Various factors affect the spread of drug in the CSF. Imbelloni et al., demonstrated that the relative density of a LA in relation to that of CSF is one of the most important factor affecting the level of analgesia after intrathecal administration of the drug.[13] Lui. et al., studied CSF densities in surgical patients at37C & reported to be 1.00021-1.0030 g/ml.[14] At 37C; morphine & clonidine are hypobaric in relation to CSF.[15] The densities of study drugs at room temperature were (HB &clonidine) were 1.0260 & 0.9930,respectively.[7,14,15] The density of mixture of 15mg HB & 45ug clonidine was estimated to be 1.0189.We administered HB first, followed by clonidine without aspiration of CSF to minimize the density effect .Desai et al., administered HB with fentanyl & morphine sequentially.[6] They hypothesized that HB & hypobaric morphine & fentanyl produce the maximal effects at their original densities. Premixing them reduces spread of morphine intrathecally & hence duration of analgesia.[6] On sequential administration drugs take their own course of spread & hence the prolonged action. The result of our study is in concordance with the result of Sachan P et al., who found rapid onset of both sensory & motor block, delayed sensory block regression & motor block resolution also the prolonged postoperative analgesia in sequential group. Also the mean time to reach maximal sensory height & complete the motor block were less in group S compared to group M. This is due to alteration in density & spread of the drug on premixing which is avoided on sequential administration. Intrathecal clonidine when combined with LA significantly potentiates the intensity & duration of motor blockade as α-2 agonists induce cellular modification in the ventral horn of spinal cord & facilitate the local anesthetic action, & prolongation in sensory block can be due to vasoconstrictive effect.[3] Gray et al., studied the effect of giving intrathecal morphine with normal saline(hypobaric) & with dextrose saline (hyperbaric).[16] They observed prolonged postoperative analgesia with hypobaric morphine solution. He stated that dextrose in a HB solution slowed the movement of morphine molecules in the CSF, reducing the exposure of supraspinal centers to morphine. Baker et al., also inferred that on increasing the baricity of intrathecal clonidine reduces the analgesia.[17] Sequential administration allows the drug to take their own course.[18]

Clonidine decreases HR by a presynaptic mediated inhibition of norepinephrine release, partly by vagomimetic effect & depressing atrioventricular nodal conduction after systemic absorption.[17,19] We found fall in HR from baseline in 8 patient (26.67%) in group S compared to 4(13.34%)in group M similar to study by Sachan P et al. One patient in group M & 2 in group S had bradycardia but none of the patient required atropine. We observed hypotension 13.24% in group M & 16.63% in group S. But only 2 patients in group M & 3 in group S needed ephedrine, rest of the patients were managed with rapid crystalloid infusion. Clonidine causes sympatholysis & reduces arterial blood pressure through action at nucleus tractus solitarius & on sympathetic preganglionic neurons.[19,20] we found sedation in both the groups which was statistically insignificant. Clonidine produces sedation in dose dependent manner by action on locus ceruleus. In stress situation, it reduces neurohumoral hormone secre-

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tion (norepinephrine, epinephrine, ACTH, cortisol) secondary to sympathoadrenal hyperactivation which is helpful for anxiolysis.[19] Clonidine produces analgesia by blocking conduction of A delta & C fibers & also intensifies conduction block of local anaesthetic.[19] None of the patient had respiratory distress, dryness of mouth which are dose dependent side effects of clonidine.[4,19]

The limitation of the present study is the small number of cases. Though our results tend to suggest that the sequentially administered intrathecal clonidine shows early onset, prolonged sensorial & motor action with prolonged postoperative analgesia to obtain a definite result, study with enrolment of larger number of patients is required.

CONCLUSION: Sequential administration of intrathecal clonidine with hyperbaric bupivacaine as compared to premixed produces rapid onset, delays the two segment sensory block regression, prolongs sensorial & motor action without any significant side effect.

Table 1: Patient's characteristics

Parameters	Group M	Group S	P Value
Age (Years)	35.21± 9.92	35.7±10.81	NS
Weight (kg)	61.36±5.2	60.52±5.2	NS
Gender (M/F)	18/12	16/14	NS
ASA (I/II)	13/17	10/20	NS
Height(cm)	158±1.3	156±1.8	NS
Duration of surgery (min)	114.2± 32.4	118.4± 22.4	NS
Type of surgery			
Tibia ORIF	7	6	NS
Tibia I/R	5	4	NS
Femur ORIF	8	7	NS
Femur I/R	5	6	NS
Knee Arthroscopy	5	6	NS

NS: Not significant, ORIF: Open reduction and internal fixation, I/R: Implant removal

Table 2: Characteristics of subarchnoid block

	Group M (Mean ±SD)	Group S(Mean ± SD)	P Value
Onset of sensory block (sec)	57±16.52	56±16.48	0.8
Time to reach maximal sensory block height (min)	6.4±2.21	5.2±2.18	0.039
Maximal sensory block height (T) median	T_4	T_5	0.5
Two segment regression time(min)	126.62±22.54	211.56±24.76	0.000
Total duration of analgesia(min)	366.32±32.35	554.28±34.28	0.000
Onset of motor block (Bromage1) min	1.22±0.33	1.16±0.32	0.442
Time to complete motor block (Bromage3) min	8.16±2.10.	6.11±2.14	0.000
Resolution time of motor block (min)	269.28±36.24	356.32±32.23	0.000

Table 3: Adverse events

Adverse events	Group M, N (%)	Group S, N (%)	P Value
Bradycardia	1(3.33%)	2(6.67%)	NS
Hypotension	4(13.24%)	5(16.67%)	NS
Respiratory depression	0	0	NS

REFERENCE

1 .Grande RP, Wig J, Yaddanapudi LN. Evaluation of bupivacaine- clonidine combination for unilateral spinal anesthesia in lower limb orthopedic surgery. J Anaesth Clin Pharmacol 2008;24:155-8. | 2 .van Tuijl I, Giezeman MJ, Braithwaite SA, Hennis PJ, van Klei WA. Intrathecal low dose hyperbaric bupivacaine-clonidine combination in outpatient knee arthroscopy: A randomized controlled trial. Acta Anesthesiol Scand 2008;52:343-9. | 3.Dobrydnjov I, Axeisson K, Thorn SE, Matthiesen P, Klockhoff H, Olmstrom B, et al. Clonidine combined with small dose bupivacaine diring spinal anesthesia for inguinal herniorrhapy: A randomized double-blinded study. Anesth Analg 2003;96:1496-503. | 4.Sethi BS, Samuel M, Sreevastava D. Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. Indian J Anaesth 2007;51:415-9. | 5.Greene NM. Distribution of local anesthetic solution within the subarchnoid space. Anesth Analg 1985;64:715-30. | 6.Desai S, Lim Y, Tan CH, Sia AT. A randomized controlled trial of hyperbaric bupivacaine with opioids, injected as either a mixtyre or sequentially, for spinal anaesthesia for caeserian section. Anaesth Intensive Care 2010;38:280-4. | 7.Sachah P, Kumar N, Sharma JP, Efficacy of premixed versus sequential administration of clonidine as an adjuvant to hyperbaric bupivacaine in cesarean section 2014;8:20-5. | 8. Thakur A, Bhardwaj M, Kaur K, Dureja J, Hooda S, Tarak S. Intrathecal clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing inguinal herniorrhaphy: A randomised double blinded study. J Anaesthesiol Clin Pharmacol 2013;29:66-70. | 9.Gabriel JS, Gordin V. Alpha 2 agonists in regional anesthesia and analgesia. Curr Opin Anaesthesiol 2001; 14:751-3. | 10.Persec J, Persec Z, Husedzinovic I. Postoperative pain and systemic inflammatory stress response after preoperative analgesia with clonidine or levobupivacaine: a randomized controlled trial. Wein Klin Wochenschr 2009;121:558-63. | 11.Romero-Sandoval A, Eisenach JC. Clonidine reduces hypersensitivity and alters the balance of pro and anti-inflammatory leukocytes after local injection at the site of inflammatory neuritis. Brain Behav Immun 2007;21:569-80. | 12. De Kock M, Gautier P, Fanard L, Luc Hody J, Lavandhomme P, Intrathecal Ropivacaine and Clonidine for Ambulatory Knee Arthroscopy: A Dose-Response Study. Anesthesiology 2001;94:574-8. | 13. Imbelloni LE, Moreira AD, Gaspar FC, Gouveia MA, Cordeiro JA. Assessment of the densities of local anesthetics and their combination with adjuvants. An experimental study. Rev Bras Anesthesiol 2009;59:154-65. | 14. Lui AC, Polis TZ, Cicutti NJ: Densities of cerebrospinal fluid and spinal anesthetic solutions in surgical patients at body temperature. Can J Anaesth 1998; 45: 297 – 303. | 15. Richardson MG, Wissler RN. Density of lumbar cerebrospinal fluid in pregnant and non-pregnant humans. Anesthesiology 1996;85:326-30. | 16. Gray JR, Fromme GA, Nauss LA, Wang JK, Ilstrup DM. Intrathecal morphine for post- thoracotomy pain. Anesth Analg 1986;65:873-6. | 17. Baker A, Klimscha W, Eisenach JC, Li X-H, Wilding E, Menth-Chiari WA, et al. Intrathecal clonidine for postoperative analgesia in elderly patients: The influence of baricity on hemodynamic and analgesic effects. Anaesth Analg 2004;99:128-34. | 18. Atalay C, Aksoy M, Aksoy AN, Dogan N, Kursad H. Combining intrathecal bupivacaine and meperidine during caesarean section to prevent spinal anesthesia-induced hypotension and other side-effects. J Int Med Res 2010;38:1626-36. | 19. Eisenach JC, De Kock M, Klimscha W. α-2 Adrenergic agonists in regional anesthesia. Anesthesiology 1996;65:655-74. | 20.Strebel S, Gurzeler AJ, Schneider CM. Small dose intrathecal clonidine and isobaric bupivacaine for orthopedic surgery: A dose response study. Anesth Analg 2004;99:1231-8. |