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Comparative Evaluation of Intrathecal Administration of Preservative free Levobupivacaine Alone and with Clonidine in Different Doses in Patients Undergoing Infraumbilical Surgeries

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Abstract

Introduction: This study was done to look for the onset of effect and hemodynamic alterations with levobupivacaine in spinal anesthesia and to compare the effect of clonidine on onset and duration of levobupivacaine when given intrathecally in two different doses. Adverse effects and complications associated with the use of above drugs were also studied.

Material and Methods: 75ASA I-II patients with age group 18-60 years undergoing infraumbilical surgeries were randomized to one of the three groups. Patients in Group 1 (L) received 15 mg (3.0 ml of 0.5%) preservative free levobupivacaine with 0.4 ml normal saline. Patients in group 2 (LC1) received 15 mg (3.0 ml of 0.5%) levobupivacaine with clonidine 30 µg (0.2 ml) and 0.2 ml normal saline. Group 3 (LC2) received 15 mg (3.0 ml of 0.5%) levobupivacaine with clonidine 60 µg (0.4 ml). Onset and duration of sensory and motor block, maximum sensory level achieved, sedation levels, hemodynamic parameters and adverse effects were recorded.

Results: Clonidine significantly shortened the onset of sensory and motor block and prolonged the time to two segment regression and regression of motor block to modified Bromage 0. In addition group LC2 had higher sedation scores. There was higher incidence of hypotension, bradycardia and respiratory depression in group LC2.

Conclusion: Intrathecal Clonidine in a dose of 30 µg significantly prolongs the anesthetic effects of intrathecal levobupivacaine without significant side effects. So, 30 µg is the preferred dose of clonidine over 60 µg, when used as an adjuvant to levobupivacaine in spinal anesthesia.

Keywords: Clonidine; levobupivacaine; Intrathecal; Spinal anesthesia.

Introduction

The most common and safe Anesthesia for infraumbilical surgeries is spinal Anesthesia because of its rapid onset, superior blockade, less failure rates and cost effectiveness.[1,2] Levobupivacaine is an amide local anesthetic that is the *S* (–) isomer of the racemic bupivacaine.[3,4] Levobupivacaine has been recently introduced in clinical practice because of its lower toxic effects as compared to bupivacaine.[5,6] Various adjuvants have been used with the local anesthetics to improve the block characteristics. Intrathecal clonidine produces dose

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dependent analgesia and prolongs the duration of intrathecally administered local anesthetics and has potent antinociceptive properties.[7,8] In the present study clonidine is used in combination with levobupivacaine in spinal Anesthesia.

Material and Methods

The study was conducted in ASA I-II patients with age group 18-60 years undergoing infraumbilical surgical procedures. Informed consent was obtained from the patients and approval was taken from the ethical committee of Indira Gandhi Medical College, Shimla. Exclusion criteria was patient with history of allergy to amide local anesthetics or clonidine, bleeding or coagulation abnormalities, peripheral neuropathy, raised intracranial pressure, demyelinating central nervous disorders, local sepsis, spinal deformities, uncooperative and unwillingness of the patient. Patients were randomly divided into three groups of 25 patients each. After routine premedication and nil per oral protocols patients were taken in the operation theatre and standard monitors were attached. Spinal Anesthesia was given to all the patients in L_3-L_4 interspace with 26 gauge quincke needle. All the patients received 3.4 ml of drug intrathecally. Patients in group 1 (L) received 15 mg (3.0 ml of 0.5%) preservative free levobupivacaine with 0.4 ml normal saline. Patients in group 2 (LC1) received 15 mg (3.0 ml of 0.5%) levobupivacaine with clonidine 30 µg (0.2 ml) and 0.2 ml normal saline. Group 3 (LC2) received 15 mg (3.0 ml of 0.5%) levobupivacaine with clonidine 60 µg (0.4 ml). The onset of sensory block was assessed from the time of injecting drug into subarachnoid space till complete analgesia at the level of T_{10}. Level of sensory block was checked bilaterally by pin prick method with 23- gauge hypodermic blunt needle and dermatomal level was tested every 2 minutes until the highest level was stabilized for four consecutive tests. Maximum level achieved was noted. After that sensory level assessement was done every 10 minutes till there was two segment regression of the block. The onset of motor block was assessed every 2 minutes till complete motor block achieved as per Modified Bromage Scale (1- total motor block, 2- patient can only move his/her feet, 3- patient can move his/her knees, 4- patient can lift his/her leg but cannot hold the position, 5- No hip function, patient can lift and hold his/her leg for 10 seconds, 6- No motor block).

Blood pressure (systolic blood pressure, diastolic blood pressure, mean arterial pressure), heart rate and peripheral oxygen saturation (SpO_2) were measured every 3 minutes for first 30 minutes, then every 5 minutes for next 30 minutes and every 10 minutes for next 1 hour. Vitals of all the patients were monitored for 2 hours after giving spinal Anesthesia. Oxygen was given by a face mask if the pulse oximeter reading decreased below 90%. Duration of sensory block was taken as the time from the onset of the sensory block to the time taken for two segment regression of the block from the maximum sensory block level. The duration of motor block was taken as the time from complete motor block (modified bromage 1) to time when lower limb can be moved freely (modified bromage 6). The degree of sedation was measured with a four point verbal rating scale (1- no sedation, 2-light sedation, 3-somnolence, 4-deep sedation). Hypotension (mean blood pressure recording less than 20% of baseline) if any, was treated with the help of intravenous fluid bolus and incremental doses of vasopressor agent mephentermine 6 mg intravenous. If bradycardia (heart rate less than 50 beats per minute) occured, it was treated with injection atropine 0.6 mg intravenous. Respiratory depression (if RR <8 breath/min or SpO_2 <90%) was treated with oxygen supplementation. Nausea, vomiting, shivering or any other side effects were followed up post operatively for 24 hours and treated upon. Postoperative pain was assessed with the help of visual analogue scale (VAS). For post operative pain (VAS >4) injection tramadol 100 mg i.v. was given as rescue analgesia and then can be repeated four hourly if needed (maximum daily dose 400 mg/day). Analysis of the data between groups was performed using one way analysis of variance test (ANOVA test), student t-test and chi-square test (whichever was applicable). $P<0.05$ was considered statistically significant.

Results

All the three groups were comparable in age, weight and sex distribution (Table 1). The baseline parameters (heart rate, blood pressure, SpO_2) were found to be comparable and the differences were statistically insignificant (p-value >0.05).

The onset of sensory as well as motor block was faster in the group LC1 and LC2 and this difference was found to be statistically significant (p-value 0.01) (Table 2). Maximum level of sensory block achieved was noted in each group. The difference of maximum level of sensory block was highly significant between the groups (p-value <0.05). The difference of the time for two segment regression from highest sensory level was highly significant (p-value 0.00) (Table 2).

The onset of motor block was also faster in group LC2 as compared to LC1 and L and the difference was significant (p-value 0.02) (Table 2). Difference of the mean duration of motor block in group L, LC1 and LC2 was highly significant statistically (p-value 0.00) (Table 2).

100% patients in group L had sedation score 1. 44% patients in group LC1 had sedation score 3. 32% patients in group LC2 developed deep sedation and had sedation score 4. The difference of the sedation scores was highly significant between the groups (p-value 0.00).

None of the patient in any of the three groups experienced nausea, vomiting or shivering. None of the patient in group L and LC1 experienced bradycardia. 24% patients in group LC2 experienced bradycardia. The difference was highly significant (p-value 0.001). 12% patients in group L, 56% patients in group LC1 and 68% patients in group LC2 developed hypotension. The difference was highly significant (p-value 0.00) (Table 3). 8% patients in group LC1 and 52% patients in group LC2 developed respiratory depression and was treated with oxygen supplementation. None of the patients in group L had respiratory depression. p-value was 0.000 which was highly significant (Table 3).

Doses of intravenous mephentermine given for treatment of hypotension was more in group LC2 as compared to L and LC1 (p-valve 0.04). Doses of intravenous atropine given for treatment of bradycardia was also more in group LC2 as compared to L and LC1 with p-valve of 0.01.

Table 1: Demographic Data

Parameter		Group L	Group LC1	Group LC2	p-value
Age (years)	Mean ±S.D.	45.44±13.79	42.20±14.68	49.60±17.56	0.46
Weight(Kg)	Mean ±S.D.	59.64±9.29	62.44±8.13	59.48±7.58	0.24
Sex	Male	21	18	20	0.573
	Female	4	7	5	

Table 2: Anesthetic characteristics of spinal block

Parameter	L	LC1	LC2	p
Onset of sensory block (in minutes)	3.72±0.84	3.64±0.90	2.96±0.97	0.01*
Time to achieve maximum sensory level (in minutes)	10.60±2.16	11.64±1.99	10.48±3.73	0.14
Maximum level of sensory block achieved	T_6 (T_5-T_8)	T_5 (T_4-T_6)	T_4(T_3- T_6)	0.00**
Time for two segment regression (in minutes)	145.56±11.47	216.04±14.69	229.96±19.09	0.00**
Onset of motor block(minutes)	4.84±1.41	4.68±1.40	3.88±1.71	0.02*
Duration of motor block (minutes)	226.52±29.83	335.88±42.73	422.24±58.86	0.00**
Sedation scores	1	2 (1-3)	3 (2-4).	0.00**

Table 3: Assessment of side effects

Parameter	Group L		Group LC1		Group LC2		P
	Number	%age	Number	%age	Number	%age	
Nausea	0	0	0	0	0	0	NS
Bradycardia	0	0	0	0	6	24	0.001**
Hypotension	3	12	14	56	17	68	0.00**
Shivering	0	0	0	0	0	0	NS
Respiratory depression	0	0	2	8	13	52	0.00**

Discussion

Spinal Anesthesia provides adequate surgical Anesthesia and prolonged post-operative pain relief. It also blunts autonomic, somatic and endocrine responses to surgical stimulus.[1] Levobupivacaine has similar pharmacodynamic properties to racemic bupivacaine but has a documented reduced central nervous system and cardiovascular toxicity.[9,10] In the study conducted by Onur O et al.,[9] in which different doses of intrathecal levobupivacaine (7.5 mg, 10 mg, 12.5 mg and 15 mg) were used they found that 15 mg would be an ideal dose for lower limb orthopaedic surgeries. Since this dose of 15 mg provides an adequate sensory and motor block for lower limb orthopaedic surgical procedures, we selected 15 mg of levobupivacaine. It has also been found that 3 ml of 0.5% plain levobupivacaine (15 mg) has a density of 1.00419 at 37°C, (that is the body temperature) and behaves like an isobaric drug even at this temperature.[11] Hence it may be an ideal drug for lower limb orthopaedic surgeries and being an isobaric drug, it can produce a longer duration of sensory block.[12,13]

Levobupivacaine has been introduced recently in India in 2012 and is available as 0.5% isobaric 4 ml ampoules for intrathecal use. Not many studies have been done regarding its intrathecal route of administration in India. A study was required to know its efficiency for spinal Anesthesia. It is known that a single injection of levobupivacaine will not produce a prolonged duration of post-operative analgesia. Hence addition of a drug which can prolong the analgesic effect of levobupivacaine will be required.[14] Various adjuvants like opioids, benzodiazepines, neostigmine and alpha-2 agonists have been used to prolong the duration of spinal analgesia. Each of these adjuvants has their own side effects like opioids producing respiratory depression, nausea, vomiting, and pruritus[15] etc; neostigmine producing hypertension and tachycardia[16]; benzodiazepines like midazolam producing excessive sedation.[17] Clonidine is a partial alpha-2 agonist which is used as an analgesic supplement through epidural and intrathecal routes along with local anesthetics.[18,19] It is known to increase both sensory and motor block of local anesthetics.[20] The analgesic effect following its intrathecal administration is mediated spinally through activation of post synaptic alpha-2 receptors in the substantia gelatinosa of spinal cord.[20,21] The rationale behind intrathecal administration of clonidine is to achieve a high drug concentration in the vicinity of alpha-2 adrenoreceptors in the spinal cord and it works by blocking the conduction of C and A delta fibres, increases potassium conductance in isolated neurons in vitro and intensifies conduction block of local anesthetics.[22,23] When Clonidine is combined with bupivacaine for spinal Anesthesia, it has been found to prolong post operative analgesia.[24] Clonidine in the dose of 1 µg/kg body weight along with bupivacaine has been found to prolong the post operative analgesia but has produced significant perioperative hypotension and bradycardia.[25] Various studies have used smaller doses of intrathecal clonidine with bupivacaine and have obtained varying results. There are many conflicting reports regarding the smaller doses of intrathecal clonidine (15 µg – 45 µg) as supplement to local anesthetic agents. It has been found to produce prolongation of post operative analgesia with minimal cardiovascular complications.[26,27]

Not many studies have used clonidine along with the local anesthetic levobupivacaine in spinal Anesthesia for infraumbilical surgeries. Hence a study was undertaken to find out the effectiveness of isobaric 0.5% levobupivacaine in subarachnoid block in infraumbilical surgeries and also to find out the effect of different doses of clonidine as an adjuvant to levobupivacaine.

Conclusion

Clonidine shortens the time of onset and prolongs the duration of sensory and motor block. 30 µg clonidine is an attractive alternative as an adjuvant to spinal levobupivacaine in surgical procedures especially in those that need quite long time with minimal side effects and excellent quality of spinal analgesia.

Conflicts of interest: There are no conflicts of interest.

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