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Original Research Paper

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A COMPARATIVE RANDOMISED STUDY OF EFFECT OF INTRATHECAL CLONIDINE AS AN ADJUVANT TO INTRATHECAL LEVOBUPIVACANE AT DIFFERENT DOSES TO DETERMINE THE OPTIMUM DOSE IN LOWER ABDOMINAL SURGERIES

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ABSTRACT

Background and Aims: Clonidine is widely used as an adjuvant to spinal anaesthesia to improve quality of anaesthesia but with haemodynamic side effects with increasing dose. We have conducted a study to observe the effects of Clonidine as an adjuvant to intrathecal isobaric levobupivacaine at different doses in terms of time to onset, duration and quality of block along with hemodyanamic changes to determine the optimal dose. **Methods:** Seventy-five patients were divided randomly in three groups of 25 patients each who got admitted for lower abdominal surgeries. **Group LC15:** 0.5% 15mg 3 ml levobupivacaine with Clonidine 15µg (0.1ml) and 0.4cc of normal saline. Group LC30: 0.5% 15mg 3 ml levobupivacaine with Clonidine 30µg (0.2ml) and 0.3ml of normal saline. **Group LC45 :** 0.5% 15mg 3 ml levobupivacaine with Clonidine 45µg (0.3ml) and 0.2ml of normal saline. volume of drug was equal in all three groups. **Results:** The time to onset of sensory as well as motor block was decreased in dose dependant manner, was least in group LC45 and most in group LC15 (Pvalue=0.0001). The two segment regression, duration of analgesia was most in group LC45 (Pvalue=0.0001). There was significant fall (>80%) in blood pressure in group LC45 seen in 9 cases out of 25 (36%) than in group LC30 seen in 3 cases out of 25 (12%) and LC 15 seen in 0 cases. **Conclusion:** the optimum dose of Clonidine as an adjuvant to spinal anaesthesia given with intrathecal isobaric levobupivacaine 0.5% was 30µg with dose dependant decrease in duration to onset of sensory and motor blockade and prolonged postoperative analgesia with haemodynamic stability most with 30µg dose.

KEYWORDS :

INTRODUCTION:

Central neuraxial blockade is the most popular technique of anaesthesia for lower abdominal surgeries. It is having several advantages like easy technique, economical and provides good quality of anaesthesia. It avoids the risks of intubation and aspiration, provides early ambulation. It is almost devoid of pharmacological effects on patient. By altering the drug dose different level of block can be achieved.Spinal block has well defined end points and anaesthesiologist can produce reliable blocks with single injection is the reason behind popularity of subarachnoid block.The wide range of local anaesthetics and additives allow control over onset, level and duration of spinal anaesthesia. The local anaesthetic solution distribution within the space determines the extent of neural blockade produced by spinal anaesthesia. Bupivacaine is most commonly used local anaesthetic drug for spinal anaesthesia but cardio-toxicity is that the limiting factor.Levobupivacaine is having similar clinical profile with less cardio-toxicity than Bupivacaine and is gaining popularity.[1] It has demonstrated less affinity and strength of inhibitory effect on the inactivated state of cardiac sodium channels than the Bupivacaine and faster protein binding rate.[2]. To provide good quality of intra-operative anaesthesia with post-operative analgesia different additives like Opioids, Ketamine, Midazolam, Neostigmine and μ-2 adrenergic agonist are used.[3]Opioids may cause pruritus, nausea, vomiting, urinary retention and respiratory depression. Midazolam causes neurotoxicity[4]. Clonidine is a selective partial μ- 2 adrenergic agonist provides effective, prolonged and dose dependent analgesia with a consequently decreased requirement of supplemental analgesics[5][6] This study was planned to compare the effect of Clonidine on quality of anaesthesia at doses 15 μg, 30 μg and 45 μg on lower abdominal surgeries including general surgical and gynaecological and urological procedures done under spinal anaesthesia, to determine the optimum dose that is devoid of significant haemodynamic disturbances with significant improvement in quality of anaesthesia.

METHODS AND MATERIALS:

This was a prospective randomised comparative double blind study. Approval from institutional ethics committee was obtained. Seventy-five patients who got admitted for elective and emergency lower abdominal surgeries in a tertiary care centre, a government medical college, in tier 2 city,ASA 1 and 2 who gave consent and more than 18 and less than 60 years of age, of either sex posted for elective lower abdominal surgeries were included in the study. Patients with contraindications to spinal anaesthesia and haemodynamically unstable patients were excluded from study. Sample size was determined considering Maheshwari et al* as reference study considering the assumptions: Confidence interval 95% Power of test 80%.For intervention study with 3 groups for comparison, sample size cake out to be 74.For convenience of calculation it was taken as 75 and divided in three groups of 25 each.Patients were divided in three groups.Group 1 (LC 15 group) was injected with 0.5% levobupivacaine 15mg (3cc) with Clonidine 15 μg (0.1cc) and 0.4cc of normal saline.

Group 2 (LC30 group) was injected with 0.5% levobupivacaine 15mg with 30 μg (0.2cc) of Clonidine and 0.3cc normal saline. Group 3 (LC45 group) was injected with inj. Levobupivacaine 15mg (3cc) with 45 μg (0.3cc) of Clonidine plus 0.2 cc of normal saline.

Total volume of drug injected intrathecally remained constant (3.5ml).After taking written informed consent from the patients, Anaesthetic procedure was briefly explained to the patient. After taking patient inside operating room monitors were attached, a single 18G canula was taken on non dominant upper limb. Routine monitors like non invasive blood pressure monitoring, SPO2 and 5 leads electrocardiogram were used. Patient vitals were continuously monitored by observer anaesthetist and recorded. Patients were co loaded with Ringer's lactate at the rate of 4ml/kg/hr. Patient was made left lateral on operating table. After

cleaning and draping under all aseptic precautions subarachnoid space was reached by 23G quincke needle in L3-L4 intervertebral space by blind loss of resistance technique. Drug was injected at the speed of 0.2ml per second and patient was made supine immediately. After injection, immediately stopwatch was started on cellular phone or machine monitors, sensory and motor block assessment was performed and listed every minute after infusion for 10 minutes and from then on every 15 minutes until first rescue analgesic is given in PACU.

Time to onset of sensory and motor block, Time to two segments regression,Time to first rescue analgesic were noted in seconds. Sensory assessment was done by using non penetrating pointed tester and motor block assessment was done with modified bromage scale. Table 1.Intraoperative vitals including pulse rate, non invasive BP, and SPO2 was noted every minute till 10 minutes then every 5 minutes for 30 minutes then 10 minutes for 60 minutes then 15 minutes thereafter till first rescue analgesic is given. Hypotension with blood pressure drop of greater than 80% of the baseline was treated with Inj. Mephentermine 6mg boluses and bradycardia with heart rate drop less than 50 per minute was treated with inj. Atropine 0.6mg bolus. Postoperative complications like vomiting, hypotension and bradycardia were also watched for. Time to first rescue analgesic was considered as the end point of the study.

Data *was entered in MS Excel. Data was analyzed in a statistical software, STATA. Descriptive statistics included mean and standard deviation for continuous variables and frequency / percentages for categorical variables. One way ANOVA was applied to compare the means of three groups. P value < 0.05 was considered statistically significant.*
Discrete variables were compared by Chi square test.

OBSERVATION AND RESULTS:

Mean age of the subjects in LC15 group is 48.16 +/- 9.78, in LC30 group is 47.12 +/- 9.50 and in This was a prospective randomised comparative double blind study.

LC45 group is 48.52 +/- 7.57.Mean age in three groups has no statistically significant difference.There were 84% males and 16% females in LC15 group, 60% males and 40% females in LC30 group and 100% males in group LC45. Table 2. Sex wise distribution of subjects in three groups has statistically significant difference. In all three groups males were significantly more than females. Figure 1. Other than sex distribution demographic profiles in all three groups were comparable Patients were posted for various types of lower abdominal and urological surgeries and were distributed as depicted in figure2. The mean Preoperative pulse rate/minute in group LC15, LC30 and LC45 was 84.84+/-6.87, 81+/-5.58 and 80.64+/-6.93 respectively. The mean systolic blood pressure in group LC15, LC30 and LC45 was 129.36+/-9.58 , 127.12+/-7.48 and 129.28+/-5.79 respectively in mm of hg. The mean diastolic blood pressure in groups LC15, LC30 and LC45 was found to be 77.12+/-5.60, 76.44+/-5.06, 79.44+/-4.16 respectively in mm of hg. Preoperative vitals were also comparable in all three groups.Table 2 The mean duration of the surgery in minutes was 81.2 +/- 17.37 in LC15 group, 93.6+/-21.81 in LC30 group and 84.8 +/- 17.76 in LC45 group had no statistically significant difference. Table 2. The mean time to sensory onset in seconds in groups LC15 was 208.04+/-6.42, in LC30 was 162.84+/-2.04 and in LC45 was 151.08+/-1.62 and was statistically significant with Pvalue = 0.0001. The mean time to motor onset in seconds in group LC15 was 270.2+/-13.75, LC30 was 252.44+/-1.5 and group LC45 was 231.28+/-1.45 which was statistically significant. (P value =0.0001). The mean time to sensory block two segment regression in seconds in group LC15 was 4344.64+/-89.09, group LC30 was 4917.72+/-133.91 and LC45 was 5521.68+/-72.13 which was statistically significant (P value= 0.0001).The mean duration of analgesia in seconds in group LC15 was 11447.5+/-228.66, LC30 was 13509.4+/-220.46 and LC45 was 14158.8+/-54.95 which was statistically significant (P value = 0.0001)Table 4. Table 3. Significant fall in blood pressure (>80% of baseline) was seen in 36% of patients in group LC45, 12% of patients in group LC30 and 0% cases in group LC15 which was statistically significant. There was no significant fall in heart rate per minute (<50/minute) in any group. Table 4.

DISCUSSION

Spinal anaesthesia has become a very popular in anaesthetic practice. Advancements in technology, improved patient satisfaction, faster recovery, increased clinician awareness, and enhanced patient safety are the reasons for the same. Adjuvants are medications that help enhance the quality and efficacy of regional techniques by acting synergistically with local anaesthetics used in regional Anaesthesia. Adjuvants are proven to quicken the onset of action, increase the duration of analgesia, improve the quality of analgesia, and decrease potential medication related adverse effects. Clonidine is selective for alpha 2 adrenergic receptors that are located on primary afferent terminals within the spinal cord and the brainstem. It is believed that clonidine also acts to block conduction of A and C pain fibers by increasing potassium conduction and subsequently enhancing the duration of action of the local anaesthetic when used in regional anaesthesia especially spinal anaesthesia [7],[8]. Clonidine may also cause vasoconstriction of the surrounding vasculature which can prolong the anaesthetic effect of the local anaesthetic by slowing its elimination from regional site [9],[10]. Many studies have been conducted to explore the intrathecal and epidural analgesic and adjuvant action of Clonidine. L. NlEMI studied the effect of intrathecal clonidine on duration of bupivacaine spinal anaesthesia, haemodynamics, and postoperative analgesia in patients undergoing knee arthroscopy.[11] They concluded addition of clonidine prolonged the bupivacaine spinal block. However, marked haemodynamic changes and sedation may limit the usefulness of intrathecal clonidine.Anil Thakur et al studied effect of Clonidine with intrathecal bupivacaine in lower abdominal and lower limb surgeries. They concluded Addition of clonidine to hyperbaric bupivacaine increased the duration of spinal anaesthesia and post operative analgesia in a dose dependent manner with minimal adverse effects.[12]In our study we observed that the time onset of sensory as well as motor block was decreased in the dose dependant manner was least in group LC45 and most in group LC15.These observations were consistent with the studies conducted by N. Maheshwari et al[13] and Ruchee Arora et al.[14]In the study by N. Maheshwari et al it was seen that when levobupivacaine is used with different doses of clonidine, onset of sensory blockade as well as motor blockade is decreased with increasing dose of clonidine.[13] The difference was in study population where this study was done on pregnant females posted for Caesarean section.A study by Ruchee Arora et al concluded that the onset to both sensory and motor blockade was decreased after adding Clonidine as an adjuvant to local anaesthetics intrathecally. [14] All the patient characteristics were also comparable. The difference was inj. Bupivacaine was used in this study and Clonidine was used at the doses of 15 μg and 30 µg. In this study it was observed that time to two segments regression was increased in dose dependant manner. It was the most with group LC45 and the least with group LC15. These observations were similar to the following study. Sudeep, N Gopal Reddy et al conducted a study that observed there was increased duration of two segment regression in group that added Clonidine to spinal anaesthesia. [15]The difference was two groups were compared with one group administered

only levobupivacaine and other group had Clonidine administered as an adjuvant. All the patient characteristics were comparable in general characteristics and age wise distribution.In this study, dose dependant prolongation of duration of analgesia was observed in groups with addition of clonidine to intrathecal isobaric levobupivacaine. It was observed the most with group LC45 and the least with LC15. It was similarly observed in following studies.Shah bhavini et al observed that the dose dependent variability in duration of analgesia and sedation after addition of Clonidine to intrathecal bupivacaine.[16] The difference was use of bupivacaine in this study and the patients were all females posted for elective Caesarian section. In a study by Ruchee Arora et al, it was concluded that the addition of intrathecal clonidine 15 µg to small dose bupivacaine increased the spread, duration of analgesia, and produced effective spinal anaesthesia with stable haemodynamic. [14] Patient characteristics were comparable. The difference was use of bupivacaine in this study and two groups were compared one with bupivacaine administered without any adjuvant and one with Clonidine as an adjuvant in low dose with bupivacaine.In this study also we found that the Clonidine 30µg given intrathecally provided better quality of anaesthesia than at 15 µg and better haemodynamic stability than 45 µg when given with isobaric levobupivacaine 0.5%.In a study by N. maheshwari et al, it was concluded that Spinal anaesthesia performed with isobaric 0.5% levobupivacaine with 30 µg clonidine (Group B) provided better haemodynamic stability, early onset of sensory and motor blockade, decreased requirement of post-operative analgesia. [13]There was no significant intraoperative or postoperative adverse effects like nausea, vomiting, respiratory depression were observed in all three groups in this study.

Anil Thakur et al through their study concluded that addition of clonidine to hyperbaric bupivacaine increased the duration of spinal anaesthesia and post operative analgesia in a dose dependent manner with minimal adverse effects.[12]It is evident from our study that levobupivacaine when used in combination with different doses of clonidine, the quality of sensory and motor block as well as analgesia was best at dose 45g but the associated haemodynamic side effects were the most with this dose. At 30 µg of clonidine, sensory and motor block was found in desirable and side effects were also less thus making it an optimum dose as an adjuvant to intrathecal levobupivacaine when used for lower abdominal and urological surgeries.

CONCLUSION:

From this study, we concluded that spinal anaesthesia performed with isobaric 0.5% levobupivacaine and Clonidine provides early onset of sensory and motor blockade, decreased requirement of post-operative analgesia in dose dependant manner. But Clonidine at the dose of 30 µg (Group LC30) provides better haemodynamic stability than at dose 45 µg (group LC45) and better quality of anaesthesia than Clonidine at the dose 15 µg (LC15) with minimal side effects. Thus the optimum dose of Clonidine as an adjuvant to spinal anaesthesia given with isobaric levobupivacaine 0.5% for lower abdominal surgeries was found to be 30 µg.

Tables:

Table 1: Modified bromage scale

1 = Complete block (unable to move feet or knees)
2 = Almost complete block (able to move feet only)
3 = Partial block (just able to move knees)
4 = Detectable weakness of hip flexion (between scores 3 and 5)
5 = No detectable weakness of hip flexion while supine (full flexion of knees)
6 = Able to perform partial knee bend

Table 2: Demographic profile of patients

	Parameter		Lc15	Lc30	Lc45	P VALUE
1)	Mean Age		48.16+/-9.78	47.12+/-9.50	48.52+/-7.57	0.00085(NS)
2)	Sex Distribution	Male Female	21 (84%) 4 (16%)	15(60%) 10(40%)	25(100%) 0(0%)	0.001(S)

Table 3: Mean time to sensory and motor onset, two segment regression and duration of analgesia

		LC15	LC30	LC45	P value
1	Mean time to sensory onset (Seconds)	208.04+/-6.42	162.84+/-2.04	151.88+/-1.62	0.0001 (S)
2	Mean time to motor onset (seconds)	270.2+/-13.75	252.44+/-1.5	231.28+/-1.45	0.0001 (S)
3	Mean time to two segment regression (seconds)	4344.64+/-89.09	4912.72 +/- 133.91	5521.68 +/-72.13	0.0001 (S)
4	Mean duration of analgesia (seconds)	11447.5+/-228.66	13509.4 +/- 220.46	14158+/-54.95	0.0001 (S)

Table 4: Number of subjects out of 25 in which intraoperative complications amongst three groups

	Complications	LC15	LC30	LC45
1	Fall in BP < 80%	0(0%)	3(12%)	9 (36%)
2	Fall in heart rate < 50	0	0	0
3	Other	0	0	0

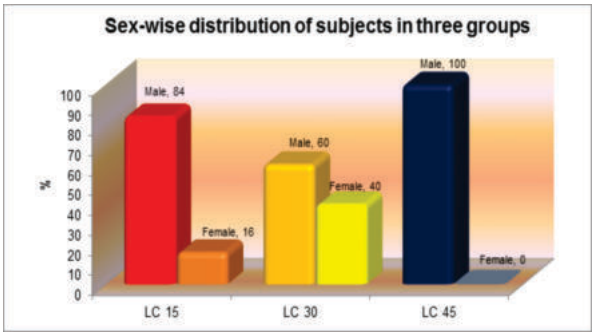

Figure 1: Sex-wise distribution of subjects in three groups

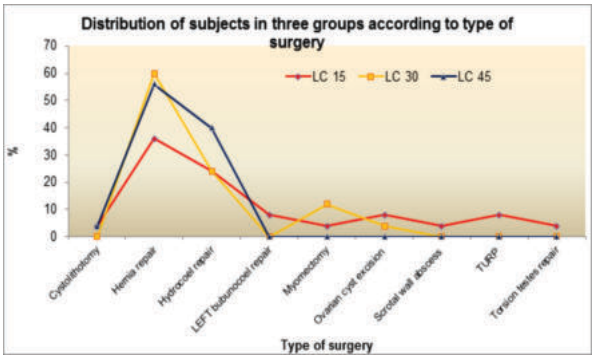

Figure 2: Types of surgery in subjects in three groups

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