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A COMPARATIVE CLINICAL STUDY OF INTRATHECAL ROPIVACAINE AND ROPIVACAINE-CLONIDINE COMBINATION FOR LOWER LIMB ORTHOPAEDIC SURGERIES

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Ropivacaine, Clonidine, sedation, analgesia, Spinal anaesthesia

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ABSTRACT: Ropivacaine is a promising drug for subarachnoid block because of its lower cardiotoxic and neurotoxic potential, but onset and duration of anaesthesia is also low and motor block is often insufficient which may lead to use of its higher doses. The aim of this randomized double-blinded study was to see whether the addition of small dose clonidine to small dose ropivacaine for spinal anesthesia prolonged the duration of postoperative analgesia while minimizing the side effects associated with higher doses of ropivacaine. We randomized 60 patients to 2 groups receiving intrathecal isobaric ropivacaine 18 mg (2.4 ml) combined with normal saline (Group R) or clonidine 30 µg (Group RC); all solutions were diluted with saline to 2.6 ml. We compared block characterstics, hemodynamic changes, post-operative analgesia and adverse effects of both the groups. Results showed that clonidine not only significantly reduced the onset time both of sensory and motor block, but also prolonged the duration. Hypotension and bradycardia was more with clonidine group during first hour. The addition of clonidine prolonged time to first analgesic request and decreased postoperative pain with minimal risk of delayed hypotension. Level of sedation and other side effects were comparable in both the groups. We concluded that addition of clonidine 30 µg to ropivacaine 18 mg produced an early and prolonged spinal anaesthesia and decrease the dose of post-operative analgesic requirement.

INTRODUCTION: Ropivacaine, an enantiomerically pure amide, has emerged as an attractive option in subarachnoid block because of its reduced CNS and cardiotoxic potential when compared to other racemic amide local anaesthetics, but this has also reduced its motor blockade intensity and post-operative analgesic duration [1]. To overcome these problems either a larger dose of ropivacaine or spinal additives can be used.

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Using additives, usually opioids or clonidine, to low doses of intrathecal ropivacaine possibly provides adequate intrathecal anaesthesia, without compromising the benefits of early mobilization and voiding, which are usually present when large dose of ropivacaine is used.

In our study, we investigated ropivacaine and clonidine combination in spinal route for lower limb orthopaedic surgeries. The α2-adrenergic agonist, clonidine, was chosen because intrathecal clonidine increases both, quality and duration of anaesthesia and increases the motor blockade due to local anaesthetic administration [2], avoiding all the side effects of opiods like pruritus and respiratory depression. Moreover, intrathecal opioids have no effect on motor blockade and may worsen urinary retention. Usual dose of intrathecal

clonidine is 1-2μg/kg. Sagiroglu et al. [3] conducted a dose finding study of intrathecal clonidine with ropivacaine in sabarachnoid block and concluded that 15μg clonidine had fewer side effects than 30μg group but motor block quality and duration of post-operative analgesia was also less. This might be helpful in short duration surgery, but in long duration surgery, where we are using subarachnoid block as only mode of anaesthesia, probably 30μg would be more advantageous.

MATERIAL AND METHODS:

After obtaining approval from institutional ethics committee sixty healthy patients of ASA physical status I and II of either sex, aged between 18–60 yrs with a height between 160- 170 cm, having body mass index (BMI) between 18.5–25 kg/m^2, scheduled for elective lower limb orthopaedic surgery were included in this study. Patients presenting for emergency surgery, pyrexia, those with allergy to study drugs or had any contraindications to spinal anaesthesia were excluded from the study.

Patients were randomly allocated to two groups of thirty each using envelope method. Group R (control group) received 0.75% isobaric ropivacaine 18 mg (2.4 ml) with 0.2 ml normal saline while group RC received the same amount of ropivacaine with 30μg (0.2 ml) clonidine.

All patients had pre-anaesthetic check up. Tab. diazepam 5 mg and ranitidine 150 mg was given orally on night before surgery. Standard NPO guidelines were followed. In operating room, monitors (electrocardiography, non invasive blood pressure, pulse oximetry) were attached and baseline values were noted. Intravenous access was established with 18G cannula and 15 ml/kg ringer lactate was preloaded. After ensuring sterile conditions, spinal anaesthesia was performed by accessing the subarachnoid space with a 25G spinal needle at L4-5 or L3-4 inter-vertebral space in sitting position. Patients received drugs according to their group. Drug syringes were prepared by an independent anaesthesiologist. Immediately after intrathecal injection patients were made supine. The anaesthesiologist performing the block was blinded to the study drugs. He independently recorded the per-operative and postoperative data. Mean arterial pressure (MAP) and heart rate (HR) were recorded at 3 minutes interval for first 30 minutes and then at an interval of 5 minutes for next 30 minutes. Thereafter these values were recorded at interval of 10 minutes for the rest of intra-operative period. Postoperatively, vitals were recorded every 15 minutes for up to 3 hours after giving spinal. Episodes of significant hypotension and bradycardia were treated with intravenous boluses of phenylephrine (50-100μg) and atropine (600μg) respectively. Sensory block level was assessed by pin prick method along the mid-clavicular line bilaterally. Motor block was assessed according to the modified Bromage scale: 0, able to move hip; 1, unable to move hip but is able to move knee and ankle; 2, unable to move hip and knee but able to move ankle; 3, unable to move hip, knee or ankle.

Surgery was allowed when sensory block of T10 level and Bromage block of scale 2 was achieved.

Time to reach T10 dermatome sensory block, highest level of sensory block and Bromage-2 motor block were recorded before surgery. Regression time for sensory block included time to 2 segment regression and regression to S2. Regression time for motor block included time taken to regress to Bromage-0. All durations were calculated considering the time of spinal injection as time zero.

Level of sedation was checked at interval of 15 minutes during intra operative period using following scale: 0, alert; 1, occasionally drowsy, easy to arouse; 2, frequently drowsy, easy to arouse; 3, somnolent, difficult to arouse.

Incidences of nausea, vomiting, pruritus, shivering, respiratory depression and urinary retention that required post-operative urinary catheterization were also recorded. Post operative sedation scores were recorded at 3 hours and 6 hours after time zero. Patients were given rescue analgesia “on demand” with intramuscular diclofenac – initial dose of 75 mg followed by 100 mg intravenous tramadol if pain remained unrelieved. Analgesic requirement for first 24 hours was “on demand” only. First as well as total analgesic demand, both were recorded. Maximum allowable dose of diclofenac was

225mg/day and for tramadol it was 600 mg/day. Total dose of analgesic requirement in first 24 hours was recorded. Software SPSS version 16 was used for statistical calculations.

RESULT:

Demographic profile and pre-operative haemodynamics of both the groups were comparable. **Table 1**

TABLE 1: MEAN DEMOGRAPHIC DATA IN GROUP R AND GROUP RC

Characteristics	Group R (n=30) (Mean + SD)	Group RC (n=30) (Mean + SD)	Test	df = 58	p value
Age (years)	36.26 ± 8.721	34.73 ± 9.317		t = 0.6580	0.5131
Height (cm)	158.76 ± 5.769	158.2 ± 5.862	Unpaired t test	t = 0.3774	0.7073
BMI (kg/m^2)	22.65 ± 1.942	22.33 ± 1.466		t = 0.7121	0.4793
Duration of surgery	89.33 ± 15.297	90.67 ± 15.57		t = 0.3363	0.7379
Male : Female	18 : 12	17 : 13	Chi square test	χ^2 = 0.686	0.7934
ASA (I :II)	11:19	9:21		χ^2 = 0.300	0.5839
Preoperative HR	86 ± 14.073	85.33 ± 9.901	Unpaired t test	t = 0.8319	0.67
Preoperative MAP	89.67 ± 9.9666	89.2 ± 10.193		t = 0.8573	0.47

df = degree of freedom $p > 0.05$ is non-significant

Characteristics of subarachnoid block are shown in **Table 2**. Onset and duration of both sensory as well as motor block was prolonged in clonidine group.

TABLE 2: COMPARISON OF SUBARACHNOID BLOCK CHARACTERISTICS.

Time in minutes	Group R Mean ± SD	Group RC Mean ± SD	t value (df = 58)	P value
Time to reach T10 level	8.43 ± 2.56	5.2 ± 2.01	5.4355	0.0001*
Time to reach highest sensory level	13.53 ± 3.76	8.76 ± 3.01	4.770	0.0001*
2 segment regression time	74 ± 18.31	113.67 ± 19.52	8.1186	0.0001*
Regression to S_2 Level	234 ± 18.12	248 ± 24.69	2.5038	0.0151*
Time to reach Bromage -2	9.3 ± 4.37	6.8 ± 2.20	2.500	0.0070*
Regression to Bromage-0	190.83 ± 20.0	239.33 ± 23.92	8.5199	0.0001*

Unpaired t –test used, df = degree of freedom * significant ($p < 0.05$)

MAP and HR were more in Group R after spinal anaesthesia. These differences were statistically significant for first one hour only. **Fig.1** and **2**

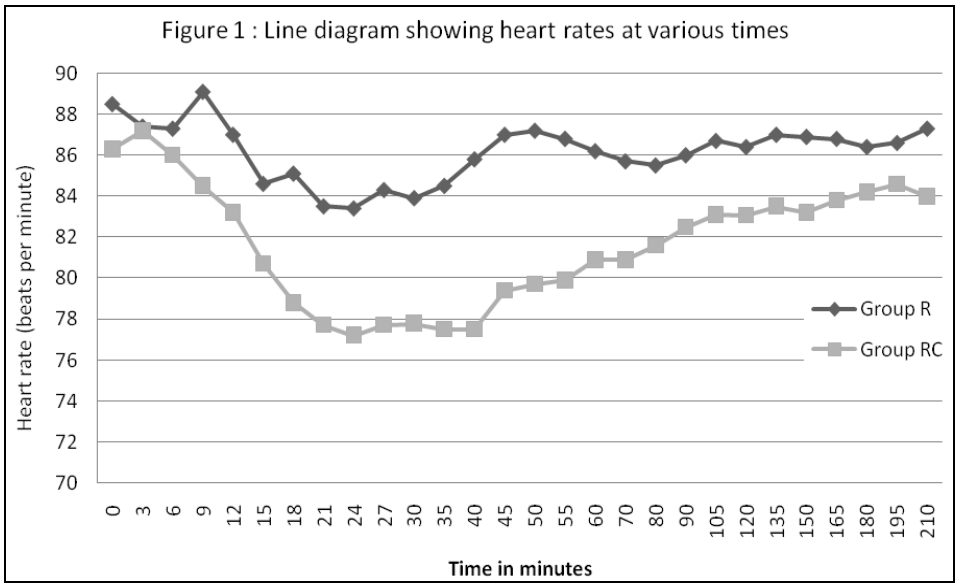

FIG.1: LINE DIAGRAM SHOWING HEART RATES AT VARIOUS TIMES

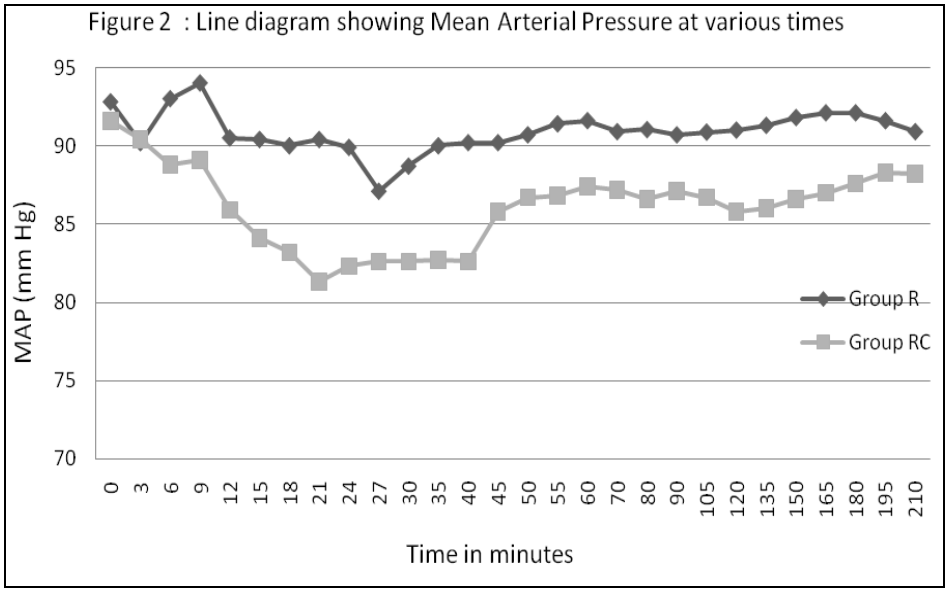

FIG.2: LINE DIAGRAM SHOWING MEAN ARTERIAL PRESSURE AT VARIOUS TIMES

Clonidine group had non-significant higher sedation scores **Table 3.**

TABLE 3: SEDATION SCORE AT DIFFERENT TIMES (NO OF PATIENTS EXPRESSED AS PER SEDATION SCORE 0/1/2/3)

Time	0 min	15 min	30 min	45 min	60 min	75 min	90 min	3 hrs	6 hrs
Group R	30/0/0/0	27/3/0/0	11/18/1/0	12/17/1/0	14/16/0/0	17/13/0/0	25/5/0/0	28/1/1/0	20/6/4/0
GroupRC	30/0/0/0	26/4/0/0	13/16/1/0	13/16/1/0	14/15/1/0	20/10/0/0	27/3/0/0	27/2/1/0	24/4/2/0/0

Clonidine in subarachnoid block delayed the first requirement of analgesic and reduced the overall demand in first 24 hours significantly. **Table 4**

TABLE 4: COMPARISON OF 'ANALGESIC DEMAND'

	Group R Mean ± S.D.	Group RC Mean ± S.D.	Test used	t value (df = 58)	p value
Time to 'First Demand' of Analgesic	233.83 ± 30.39	405 ± 85.22	Unpaired t test	10.3622	0.0001*
Total Diclofenac consumed in first 24 hours	135 ± 30.51	106.03 ± 37.59		3.2775	0.0018*

df = degree of freedom *significant ($p < 0.05$)

Adverse effect profile was comparable. **Table 5**

TABLE 5: COMPARISON OF ADVERSE EFFECT PROFILE

Adverse Effect	Group R Mean ± S.D.	Group RC Mean ± S.D	p value
PONV	3	5	0.7065
Pruritus	0	0	1.0000
Shivering	6	4	0.7306
Respiratory Depression	0	0	1.0000
Urinary Catheterization	0	0	1.0000

$p > 0.05$ is non-significant

DISCUSSION: Ropivacaine is a potent local anaesthetic with a long duration of action. The amount of local anaesthetic usually used for spinal anaesthesia is larger in relation to the minimum concentration required to block the various types of nerve fibers. Using smaller doses of ropivacaine will reduce the duration of spinal block, but sometimes a smaller number of dermatomes are blocked. Intrathecal clonidine clearly increases the duration of both sensory and motor block [4, 5] as well as postoperative pain relief. [6]

Earlier, Sagiroglu et al. [3] found that compared to plain ropivacaine, sensory block was significantly higher and prolonged in groups receiving clonidine as additive. Similarly, motor block was significantly faster and of longer duration in clonidine group, though, there were no significant differences among the groups for the maximum motor block level and the time to achieve the maximum motor block level.

Clonidine-induced potentiation of sensory block in spinal anaesthesia is mediated by presynaptic (inhibition of transmitter release) [7] and postsynaptic (enhancing hyperpolarization) [8, 9] mechanisms. Although, clonidine has a vasoconstrictive effect in large concentrations, but this has minor role in prolonging sensory block, even in usual clinical doses (1–2 μg/kg). [2, 5] Intrathecal clonidine alone, even in doses of up to 450μg, does not induce motor block or weakness.[10] In contrast, intrathecal clonidine combined with local anaesthetic significantly potentiates the intensity and duration of motor blockade. [5] Dobrydnjov et al. proposed that this could be because of α2-agonist induced cellular modification in the ventral horn of spinal cord (motoneuron hyperpolarization) that facilitated the local anaesthetic action. However, these effects may be dose related, as on adding two different doses of clonidine, they found that 30μg, but not 15μg of clonidine potentiated motor block of bupivacaine [11].

A small dose of intrathecal clonidine is not usually associated with systemic side effects such as bradycardia and hypotension.[12] Klimscha et al.[13] stated that hypotension after 20-30 minutes of injection, is due to local spinal and systemic supraspinal actions as peak concentrations occur in CSF. Lipid solubility and elimination of clonidine in CSF results in lack of delayed hypotension. Our findings corroborate with that of Dobrydnjov et al.[11]

Clonidine has been studied with local anaesthetics in various settings and has confirmed the prolongation of analgesia through all routes. In our study, we have used first demand of rescue analgesic as end point for analgesic period due to clonidine. The "first sensation of pain" at incision site can be regarded as the end of anaesthesia which is mainly due to wearing off of local anaesthetic effect. Some patients may find it mild and tolerable and may not demand for further analgesia. Delayed "request for further analgesic" seems to be wearing off effect of clonidine and thus, can help us in judging the duration of post operative analgesia.[13]

In our study we found significant delay in "first rescue analgesic demand" in clonidine group. Total consumption of analgesics in first post-operative 24 hours was also low. Ghodki et al.[14] added 30μg clonidine to intrathecal bupivacaine for laparoscopic surgeries and evaluated for shoulder tip pain. They found that incidence of shoulder tip pain was less and post operative analgesia was prolonged significantly. Clonidine significantly increased the duration and improved the post-operative analgesia in our study. Bajwa et al.,[15] Koul et al.[16] and Forster et al.[17] found similar results but these studies were done using caudal epidural route.

Sedative effect of intrathecal clonidine is dose dependent.[18] We did not find any difference in sedation levels among the two groups. Similarly, Sethi et al.[19] added clonidine (1μg/kg) to intrathecal 0.5% bupivacaine (12.5mg) and found clinically insignificant influence on sedation. D'Angelo et al. found no difference in sedation when adding 50μg clonidine to spinal bupivacaine and sufentanil.[20]

There was no significant difference in adverse effect profile of both the groups. Our results corroborate with the findings of Ghodki et al.[14]

CONCLUSION: Low dose clonidine when added to isobaric ropivacaine in subarachnoid block intensifies sensory as well as motor block but caution is required for hemodynamics especially in early intra-operative period. Post-operative analgesic requirement is reduced but sedation and other side effects are minimal.

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