Clinical Investigation

A comparative study between intrathecal clonidine and neostigmine with intrathecal bupivacaine for lower abdominal surgeries

Address for correspondence:
Dr. N. Yoganarasimha, Department of Anaesthesiology, Adichunchanagiri Institute of Medical Sciences, Mandya, Karnataka, India.
E-mail: yogaaims@gmail.com

N Yoganarasimha, TR Raghavendra, S Amitha, K Shridhar, MK Radha
Department of Anaesthesiology, Adichunchanagiri Institute of Medical Sciences, Mandya, Karnataka, India

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ABSTRACT

Background and Aims: Spinal anaesthesia requires a small volume of drug to produce profound reproducible sensory analgesia and motor blockade, but has limited duration of action. A properly chosen adjuvant to local anaesthetic agent produces the best way to achieve a better quality regional block. Hence, a study was conducted to compare the effect of intrathecal clonidine 75 μg or neostigmine 50 μg added to intrathecal hyperbaric bupivacaine, with regards to sensory characteristics, motor characteristics, haemodynamic stability and side effects. **Methods:** This was a prospective randomized experimental study in 50 patients posted for lower abdominal surgery belonging to ASA I and II status and aged between18 and 60 years. One group received intrathecal clonidine 75 μg and 2.5 ml (12.5 mg) of intrathecal 0.5% hyperbaric bupivacaine (group BC) and second group received neostigmine 50 μg with 2.5 ml (12.5mg) of intrathecal 0.5% hyperbaric bupivacaine (group BN) and they were compared with regards to sensory characteristics, motor characteristics, haemodynamic stability and side effects. **Results:** Addition of 50 μg neostigmine significantly enhanced the onset of sensory block (BN - 90 ± 15 secs, BC-160 ± 20 secs, *P* value as <0.05) and motor block (BN-110 ± 15 secs, BC-210 ± 20 secs, *P* value as <0.05) compared to clonidine. Haemodynamics were well maintained in the neostigmine group. Group BC had prolonged analgesia (362 ± 36 mins) compared to BN group (300 ± 25 mins)(*P* < 0.05) with no serious adverse effects noted perioperatively in either groups. **Conclusion:** Intrathecal clonidine with hyperbaric bupivacaine produces prolonged postoperative analgesia and intrathecal neostigmine with bupivacaine produces a good sensory and motor for the surgical procedure.

Key words: Analgesia, bromage scale, clonidine, hyperbaric, lower abdominal surgery, neostigmine

INTRODUCTION

Bupivacaine is the most commonly employed local anaesthetic for subarachanoid block, but has limited duration of action. Perioperative haemodynamic status is also a concern. Opioids, though useful as adjuvants, are associated with undesirable side effects. Hence ideal adjuvants that can be used with bupivacaine for stable intraoperative conditions and prolonging the post-operative analgesia with minimal side effects are being investigated.

Clonidine, a selective alpha (α) 2 agonist agent, routinely used as a premedicant for general anaesthesia decreases the requirement of analgesics and anaesthetic drugs intraoperatively. Intrathecal clonidine produces analgesia by indirectly inhibiting the activity of wide dynamic range (WDR) neurons.[1] Clonidine has been used by oral, epidural, spinal, perineural and parenteral routes to obtain post-operative analgesia.[2]

Neostigmine is a anticholinesterase agent which increases the acetylcholine concentrations at cholinergic synapses. Spinal neostigmine apparently activates descending pain inhibitory systems that rely on a spinal cholinergic interneuron, probably exacerbating a cholinergic tonus that is already activated during the postoperative period[3] and

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seems to be extremely efficient for alleviating somatic pain.

This study was designed to compare the intrathecal effects of two non-opioid drugs neostigmine and clonidine. The chief aims of this pharmacological comparison were to observe their effects on sensory, motor block characteristics and haemodynamic parameters.

METHODS

Over a period of 5 months duration, a prospective randomized double blinded study was performed in our institute. Ethical committee clearance was obtained and informed consent from the patients was taken. 50 patients aged between 18 and 60 years, ASA Grade I and II posted for lower abdominal surgeries were included and randomly divided into groups BN and BC using computer generated random numbers. Patients with contraindications for spinal anaesthesia, co-morbid diseases like ischemic heart disease (IHD), hypertension, bronchial asthma, diabetes mellitus and morbidly obese patients were excluded.

Group BN (n = 25) patients received 2.5 ml of 0.5% hyperbaric bupivacaine along with 0.1 ml of neostigmine (50 μg) and 0.4 ml of normal saline. And Group BC (n = 25) patients received 2.5 ml of 0.5% hyperbaric bupivacaine with 0.5 ml (75 μg) of clonidine. The patients and the monitoring anaesthesiologist were blinded to the study solutions. All the patients were premedicated on the night before surgery with tablet ranitidine 150 mg and tablet alprazolam 0.5 mg. On the day of surgery, intravenous (IV) line with 18G cannula was secured. Patients were connected to multichannel monitor displaying electrocardiogram (ECG), oxygen saturation (SPO2) and non-invasive blood pressure (NIBP) and basal readings recorded. All the patients were preloaded with 10 ml/kg of ringer lactate. Under aseptic precautions, lumbar puncture was performed using 26/27 G spinal needle at L3- L4 space. After confirming the clear free flow of cerebrospinal fluid (CSF), the study drugs were injected into the sub- arachnoid space at the rate of 1 ml given in 3 seconds, with the operation table kept flat. Patients were turned supine immediately and were given supplemental oxygen.

The following parameters were noted after SAB: Time of onset of analgesia (time taken from the injection of the drug to loss of pin prick at T10 level), cephalad spread of analgesia achieved, time taken for onset of motor blockade (time taken for complete inability to flex both the lower limbs at hip joint), quality of motor blockade assessed by Bromage scale,[4] intra operative haemodynamic monitoring (heart rate (HR), systolic blood pressure (SBP) measured immediately after SAB, 2nd min, 5th min, 10th min and every 5 min till the end of surgery), total duration of analgesia (time from the onset of analgesia to the point where the patient complained of pain at the surgical site requiring rescue analgesics or visual analogue scale (VAS)>4) and duration of motor block (complete recovery of motor power).

Hypotension was defined as reduction of SBP by more than 30% below the baseline value or SBP to less than 90 mmHg and was treated with increased rate of IV fluid infusion and vasopressor (mephentermine 6 mg). Bradycardia was defined as HR less than 60 beats per minute and was treated with atropine IV. Any other side effect associated with the administration of intrathecal clonidine and neostigmine was noted.

The data are presented as mean ± S.D. all categorical data analyzed using Fischer exact test and Chi square test as required and nominal and continuous variables using student *'t'* test. Value of $P < 0.05$ was considered significant. Statistical Package for Social Sciences (SPSS) version 10.0 for windows was used for statistical analysis.

RESULTS

The demographics and duration of surgery were comparable between the groups [Table 1].

Group BN showed early onset of sensory block (90 ± 15 secs) compared to group BC (120 ± 20 sec), ($P < 0.05$). The cephalad spread of sensory block was similar in both groups. The mean total duration of analgesia was prolonged in group BC (362 ± 32 min) compared to group BN (300 ± 25 min) ($P < 0.05$) [Table 2]. Onset of motor block was 110 ± 15 secs in group BN compared to 210 ± 20 secs in group BC ($P < 0.05$). Recovery from motor block took 185 ± 40 mins in group BN compared to 210 ± 50 mins in group BC [Table 3].

Increase in heart rate was noted in both groups following spinal anaesthesia with mean maximum increase of 18 beats/min noted at 5th min in group BN, compared increase of 14 beats/min noted at 2nd min in group BC [Figure 1]. Intraoperative blood pressure

was well maintained in the neostigmine group with mean magnitude of change of only 4 mmHg fall of systolic blood pressure noted at 40th min compared to mean maximum fall of 19 mmHg at 5th min in group BC [Figure 2]. In group BC, ten patients exhibited hypotension with SBP <80 mmHg, which occurred 15-30 min after SAB. Five patients overall required three doses of intravenous mephentermine 6 mg for hypotension. In six patients of group BC, hypotension was associated with bradycardia, which responded to Inj.atropine IV. Subsequently in all these patients there were no further changes in SBP or HR. In group BN, none of the patients developed hypotension or bradycardia.

No patients of either groups had sedation, nausea and vomiting, pruritus, post dural puncture headache or transient neurological symptoms at intraoperative period or during post-operative follow up.

Table 1: Demography

	Group BN	Group BC
Mean age (years)	28.72±9.35	37.6±4.13
Mean weight (kgs)	56.36±7.35	52.3±9.54
Male: Female ratio	18:07	11:14
Duration of surgery (min)	54.6±12.24	55.96±17.93

Group BN – Bupivacaine+Neostigmine; Group BC – Bupivacaine+ Clonidine

Table 2: Sensory characteristics

	Group BN	Group BC	*P* value
Mean onset time	98±15 sec	160±20 sec	<0.05
Median cephalad spread	T4	T4	
Mean total duration of analgesia	300.0±25 mins	362±36 mins	<0.05

Group BN – Bupivacaine+Neostigmine; Group BC – Bupivacaine+ Clonidine

Table 3: Motor characteristics

	Group BN	Group BC	*P* value
Mean time required to attain max motor blk	170±14 secs	220±40 secs	<0.05
Quality of motor blockade	Bromage grade III→100%	Bromage grade III→100%	
Duration of motor blockade	185±40 mins	210±50 mins	<0.05

Group BN – Bupivacaine+Neostigmine; Group BC – Bupivacaine+ Clonidine

DISCUSSION

Clonidine produces spinal cholinergic activation. Cholinergic interaction in spinal α-2 adrenergic receptors which are located on descending nor-adrenergic pathways produces nor-adrenaline release that causes analgesia directly and also it releases acetyl choline (Ach) to produce analgesia. Clonidine also blocks Aδ and C-fibers at lamina V, thereby producing analgesia.[2,5,6]

Clonidine has been used in varying doses from 15 μg to 300 μg intrathecally by various authors. With local anaesthetics, the maximum dose of intrathecal clonidine to be 1-2 μg/kg. Higher doses of sole clonidine is said to produce marked sedation as well as haemodynamic disturbances. Plateau effect of analgesic effect of clonidine is seen around a dose of 150μg.[7,8] In view of this, in the present study we selected a dose of 75 μg of clonidine.

In the present study, we noticed that onset for sensory blockade was hastened with addition of neostigmine, showing that neostigmine enhances action of spinally

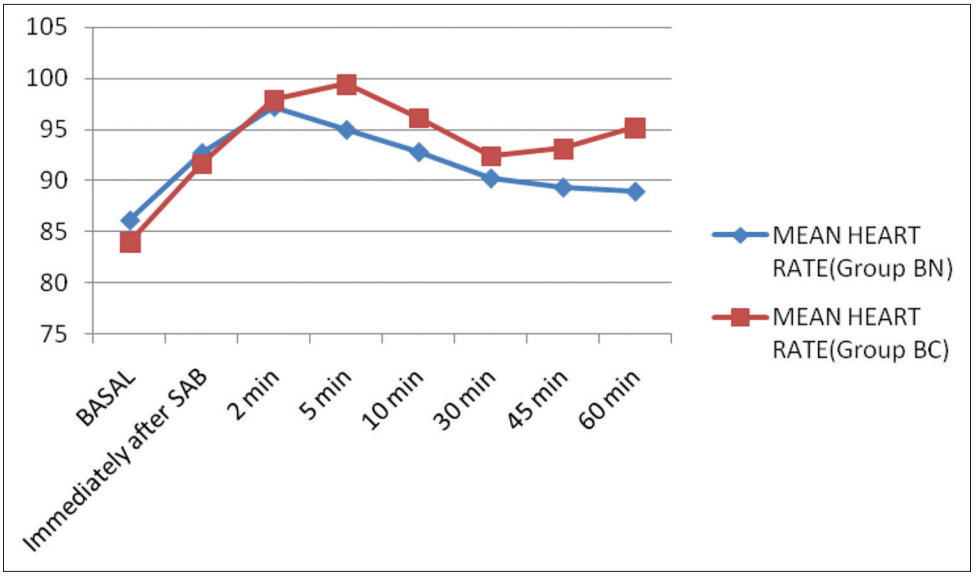

Figure 1: Heart rate comparison

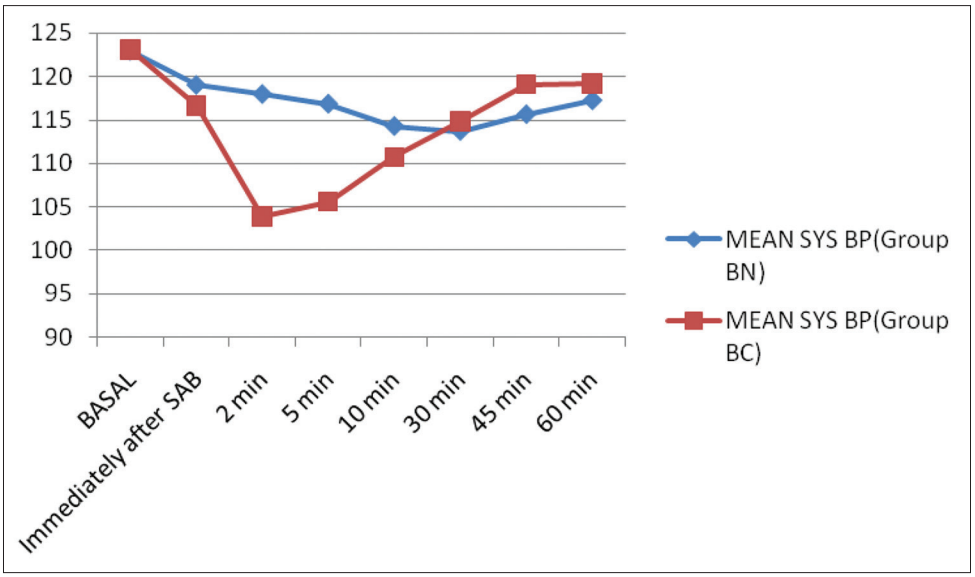

Figure 2: Systolic blood pressure comparison

administered local anaesthetics. Spinal administration of neostigmine, an acetyl cholinesterase inhibitor, inhibits breakdown of the endogenous neurotransmitter acetylcholine, thereby inducing analgesia,[9] hence it is an another alternative non opioid additive to local anaesthetics devoid of opioid- associated side effects. Intrathecally administered clonidine with local anaesthetic agents significantly prolongs the duration of analgesia.[10] We also noted that duration of analgesia was prolonged with addition of clonidine compared to neostigmine.

Clonidine is believed to prolong the motor blockade produced by local anaesthetic agents.[2] Clonidine produces local vasoconstriction by acting on vascular smooth muscle (α-receptors), which decreases absorption of local anaesthetics from sub-arachnoid space thereby prolonging the duration of action.[11-13] In addition to the potential direct inhibition of motor activity by administration of neostigmine, it was speculated that increased spinal levels of acetylcholine may augment motor block as a result of axonal conduction block from spinal bupivacaine[14] In present study, the mean time for motor block onset and the mean time taken for maximum motor blockade was significantly faster in neostigmine group than compared to group BC. Similar results were obtained in a study by Klamt *et al*.[15] Contrary to intravascular administration, intrathecal administration of neostigmine causes an increase in heart rate and blood pressure due to acetylcholine-induced stimulation of preganglionic sympathetic neurons.[16,17] In our study, there was an increase in heart rate in patients receiving intrathecal neostigmine, but intraoperative blood pressure was well maintained and this concurs with observations of Klamt.[15] The excitatory action of neostigmine on preganglionic sympathetic neurons are more pronounced after injection directly into intermediolateral cell column than after intrathecal injection further explaining the heart rate response noticed in this study.[18]

Conflicting views are given with regard to blood pressure changes following various doses of intrathecal clonidine. Smaller doses are said to produce fall in blood pressure which follows a U shaped curve, by the effect on central brain stem nucleus and pre-ganglionic sympathetic inhibition. Larger doses are said to maintain BP through its effects on peripheral vasculature.[2,3,10] There was increased incidence of hypotension following intrathecal administration of 75 μg of clonidine in the present study, but it could be easily managed with vasopressors.

Intrathecal administration of neostigmine produces well-known side effects of nausea and vomiting perioperatively due to rostral spread of neostigmine to the brainstem site.[17] Dilution of drug with local anaesthetic has probably reduced the incidence in our study. Keeping the patients in sitting posture while administering the drug or by diluting the drug with hyperbaric solution prevents the rostral spread.[19] Literature search did not provide a proper insight into the equipotent doses of clonidine and neostigmine for intrathecal use, hence this may be a limitation in the present study. More studies with adequate sample size

may be required to establish the equipotent doses of these drugs.

CONCLUSION

The use of intrathecal neostigmine 50 μg added to 12.5 mg hyperbaric bupivacaine significantly hastens the onset of sensory and motor block without prolonging the duration of analgesia compared to clonidine 75 μg. But clonidine is associated with increased incidence of hypotension.

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