

## A Comparative Study between Intrathecal Clonidine and Neostigmine with Intrathecal Bupivacaine for lower abdominal surgeries

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### ABSTRACT

**Background:** Limited duration of time has been one of the main drawback of spinal anesthesia. To avoid this, adjuvants have been added to the local anesthetic agent and has proven benefits when used intrathecally. **Aims and Objectives:** To compare the effect of intrathecal clonidine 75 µg or neostigmine 50 µg added to intrathecal hyperbaric bupivacaine, with respect to sensory characteristics, motor characteristics, haemodynamic stability and side effects. **Materials and Methods:** Our prospective study included 60 patients who were admitted for lower abdominal surgeries. The patients were randomly divided into 2 groups, with 30 in each group. Group A patients received neostigmine 50 µg with 2.5 ml of intrathecal 0.5% hyperbaric bupivacaine and group B patients received intrathecal clonidine 75 µg and 2.5 ml of intrathecal 0.5% hyperbaric bupivacaine. The parameters for comparison of 2 groups included sensory characteristics, motor characteristics, haemodynamic stability and side effects. **Results:** In Group B patients, there was a significantly enhanced onset of sensory and motor block and well maintained haemodynamics. Group A patients had prolonged analgesia. Perioperatively no serious adverse effects were noted in both the groups. **Conclusion:** Intrathecal clonidine with hyperbaric bupivacaine produces prolonged postoperative analgesia and intrathecal neostigmine with bupivacaine produces a good sensory and motor blockade for lower abdominal surgeries.

**Keywords:** Analgesia, Anaesthesia, Intrathecal, Clonidine, Neostigmine.

### Introduction

The basic purpose of giving anaesthesia is to provide good analgesia with satisfactory muscle relaxation throughout the intraoperative period and managing pain in the postoperative period. Successful management of postoperative pain may decrease morbidity and mortality, bring about early mobilization, comfort and satisfaction of patients [1,2]. Since its introduction in 1898, spinal anesthesia is one of the most accepted techniques used for elective and emergency procedures like cesarean sections, lower

abdominal surgeries, orthopedic and urological surgeries. The major advantages of spinal anesthesia apart from an awake patient are its simple technique, rapid onset of action, nominal drug cost and relatively fewer side effects. Intrathecal bupivacaine is the most commonly used local anesthetic during subarachnoid block. The main disadvantage is the insufficient duration of anesthesia and postoperative analgesia when used alone. Bupivacaine can be used for procedures lasting for about two to two and half hours, hence for surgeries which require more time, adjuvants should be added [3,4].

If the dose of intrathecal bupivacaine is increased to prolong the duration of the subarachnoid blockade, there is a risk of hypotension and bradycardia. Hence in order to prolong the duration of bupivacaine and

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postoperative analgesia, a number of adjuvants have been introduced. The other advantages being reduction in dose of local anesthetics and reduced side effects[5]. Basically adjuvants are pharmacological agents having little pharmacological effect by themselves, but can enhance or potentiate the action of other drugs when given at the same time. Many studies have been carried out to find out the efficacy of both opioids and alpha 2 adrenergic agonists like clonidine as adjuvants to intrathecal bupivacaine and found them to be effective. Alpha 2 adrenergic agonists have added advantage of absence of opioids related side effects like pruritus, nausea-vomiting, acute urinary retention and sedation[6,7].

Clonidine and neostigmine are commonly used as adjuvants to bupivacaine. Clonidine is a selective partial  $\alpha_2$  adrenergic agonist and its activation inhibits the central transmission of nociceptive impulses. Analgesic effect of clonidine is supposed due to inhibition of release of substance P[8].

Whereas the mechanism of analgesic action of neostigmine (anticholinesterase agent) is due to prevention of the breakdown of synaptically released acetylcholine, which acts on muscarinic and nicotinic receptors in the spinal cord[9].

We carried our study to compare the effect of intrathecal clonidine 75  $\mu$ g or neostigmine 50  $\mu$ g added to intrathecal hyperbaric bupivacaine, with respect to sensory characteristics, motor characteristics, haemodynamic stability and side effects.

## Material and Methods

We carried our study in 60 patients from December 2015 to November 2016, after obtaining institutional ethical committee approval. Consent was obtained from all the patients. Initially 67 patients were enrolled in the study. 7 patients were excluded as they did not meet the inclusion criteria. 60 patients were divided randomly into two groups of thirty each.

We followed the methodology used by Yoganarasimha *et al* (2014) [1]. Preanaesthetic check up and appropriate investigations were performed.

**Group A patients (n=30):** Received neostigmine 50  $\mu$ g with 2.5 ml of intrathecal 0.5% hyperbaric bupivacaine and

**Group B patients (n=30):** Received intrathecal clonidine 75  $\mu$ g and 2.5 ml of intrathecal 0.5% hyperbaric bupivacaine.

### Inclusion criteria

1. Patients undergoing lower abdominal surgeries,
2. Patients above 18 years of age and
3. Patients not allergic to the study drugs.

### Exclusion criteria

1. Patients with contraindications for spinal anaesthesia,
2. Patients with ischemic heart disease (IHD),
3. Patients with hypertension,
4. Patients with bronchial asthma,
5. Patients with diabetes mellitus and
6. Morbidly obese patients

Premedication with tablet ranitidine 150 mg and tablet alprazolam 0.5 mg was given to all the patients on the night before surgery. Patients were connected to multichannel monitor displaying electrocardiogram (ECG), oxygen saturation (SPO<sub>2</sub>) and non-invasive blood pressure (NIBP) and readings were recorded. Under aseptic conditions, 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.

The comparative parameters were noted and they were

1. Time of onset of analgesia (time taken from the injection of the drug to loss of pin prick at T10 level),
2. Cephalad spread of analgesia achieved,
3. Time taken for onset of motor blockade (time taken for complete inability to flex both the lower limbs at hip joint),
4. Quality of motor blockade assessed by Bromage scale,
5. Intra operative haemodynamic monitoring (heart rate (HR), systolic blood pressure (SBP) measured immediately, after 2 minutes, 5 minutes, 10 minutes and every 5 minutes till the end of surgery,
6. 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),
7. Duration of motor block (complete recovery of motor power) and
8. Any other side effects associated with the administration of intrathecal clonidine and neostigmine.

The data was analysed by SPSS for windows (version 17) statistical package(SPSS Inc., Chicago, IL). The data were expressed as mean  $\pm$  standard deviation (SD) and analyzed using Fischer exact test and Chi square test as required and nominal and continuous variables using student 't' test. The values of P < 0.05 was considered significant.

## Result

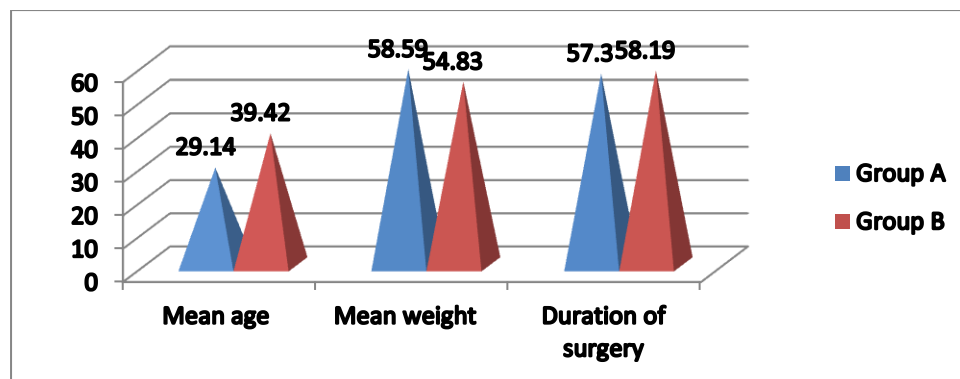
The demographic details and duration of surgery were comparable between the groups [Table 1].

**Table 1: Demographics and duration of surgery in both the groups**

Parameter	Group A	Group B	P value
Mean age (years)	29.14±9.03	39.42±4.38	<0.0001*
Mean weight (Kgs)	58.59±7.02	54.83±9.12	0.0788
Duration of surgery (minutes)	57.3±11.35	58.19±16.41	0.8078

<0.0001\*=extremely statistically significant.

**Graph 1: demographics and duration of surgery in both the groups**



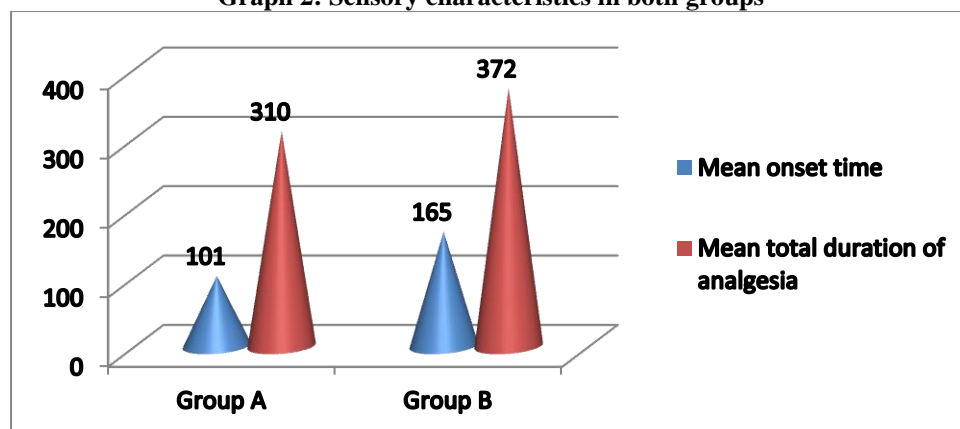
Patients in Group A showed early onset of sensory block ( $101 \pm 12$  seconds) compared to group B ( $165 \pm 18$  seconds;  $P < 0.001$ ). The cephalad spread of sensory block was similar in both groups. The mean total duration of analgesia was prolonged in group B ( $372 \pm 33$  min) compared to group A ( $310 \pm 20$  minutes;  $P < 0.001$ ) [Table 2].

**Table 2: Sensory characteristics**

Parameter	Group A	Group B	P value
Mean onset time (seconds)	$101 \pm 12$	$165 \pm 18$	<0.0001*
Mean total duration of analgesia (minutes)	$310 \pm 20$	$372 \pm 33$	<0.0001*
Median cephalad spread	T4	T4	-

<0.0001\*=Statistically significant.

**Graph 2: Sensory characteristics in both groups**



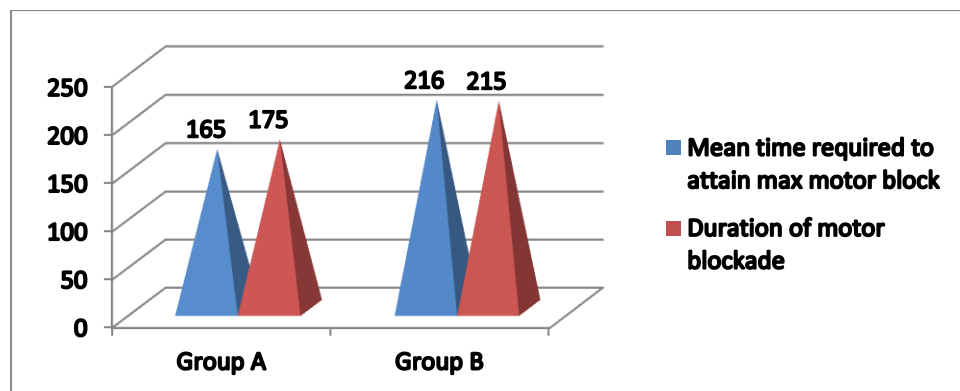
Onset of motor block was  $165 \pm 12$  seconds in group A, whereas it was  $216 \pm 36$  seconds in group B ( $P < 0.001$ ). Recovery from motor block took  $175 \pm 40$  minutes in group A compared to  $215 \pm 50$  minutes in group B [Table 3].

**Table 3: Motor characteristics in both groups**

Parameter	Group A	Group B	P value
Mean onset time (seconds)	$165 \pm 12$	$216 \pm 36$	$<0.0001^*$
Duration of motor blockade (minutes)	$175 \pm 40$	$215 \pm 50$	$<0.0001^*$
Quality of motor blockade	Bromage grade III $\rightarrow$ 100%	Bromage grade III $\rightarrow$ 100%	-

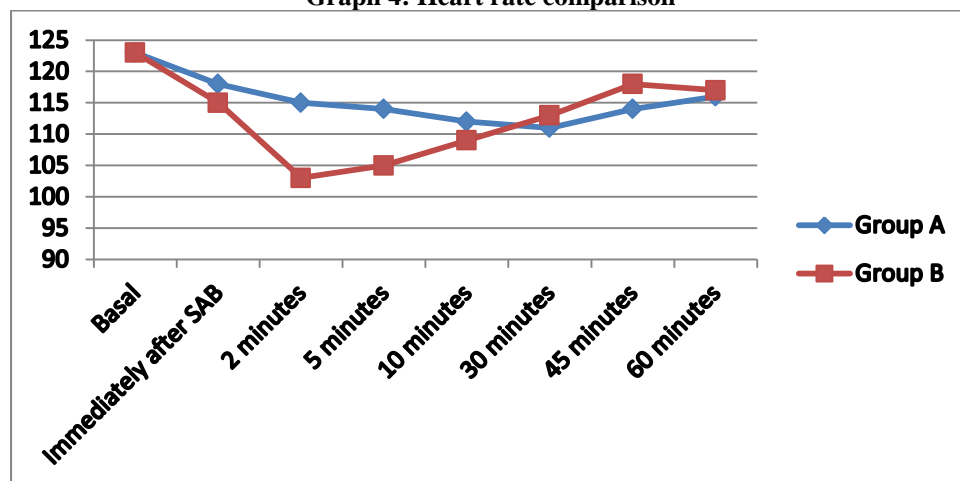
$<0.0001^*$  = Statistically significant.

**Graph 3: Motor characteristics in both groups**

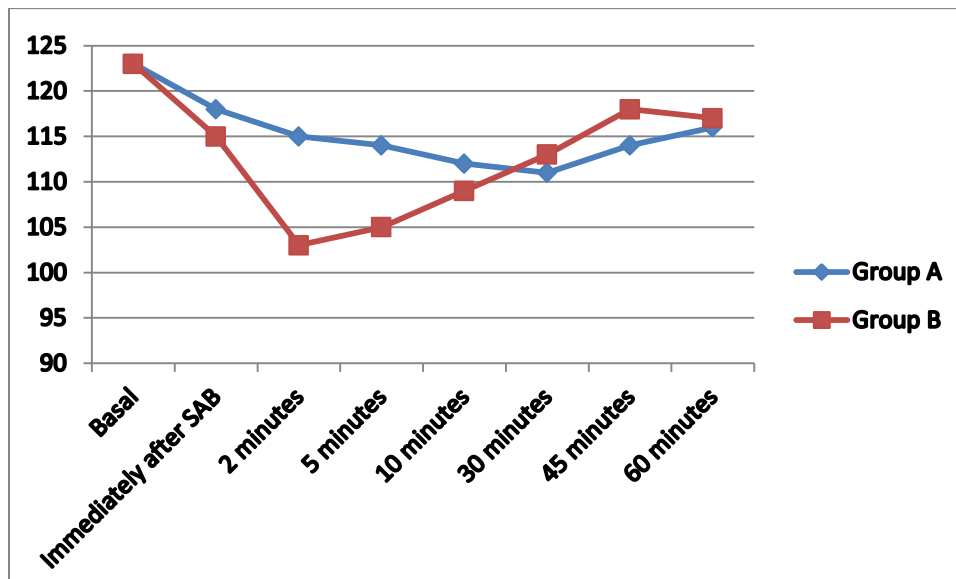


Increase in heart rate was noted in both groups following spinal anaesthesia with mean maximum increase of 18 beats/minute noted at 5<sup>th</sup> minute in group A, whereas it showed an increase of 14 beats/minutes noted at 2<sup>nd</sup> minute in group B (Graph 4 and Graph 5)

**Graph 4: Heart rate comparison**



Graph 5: Systolic blood pressure comparison



## Discussion

Anaesthetists prefer spinal anesthesia for infra umbilical surgeries like hernioplasty, appendectomy and abdominal hysterectomies, as it is the fastest, predictable and most reliable form of anesthesia. Bupivacaine is the choice for many, as it provides some analgesic effect postoperatively, but its main disadvantage is short duration of analgesia is not lengthy enough to relieve pain for extended period in postoperative setting after wearing off of the local anesthetic effect[1-3].

Anesthetic planning should include pain relief. Deleterious effects of pain during surgery or in the postoperative period are[1,3,5]

1. Sympathetic stimulation which results in increased heart rate, blood pressure, altered regional blood flow, increased oxygen consumption and
2. Stress response due to hormonal surge and depressed immune functions.

The mechanism of action of clonidine is by spinal cholinergic activation acetyl choline to produce analgesia. It also blocks A $\delta$  and C fibers at lamina V, thus producing analgesia[10,11].

Several authors used clonidine in dosages between 15  $\mu$ g to 300  $\mu$ g intrathecally. The maximum dose of intrathecal clonidine with local anaesthetics was 1-2  $\mu$ g/kg, as higher doses was shown to produce marked sedation as well as haemodynamic disturbances[10,12]. Strebel *et al* also reported that small doses of intrathecal clonidine ( $\leq$  150  $\mu$ g) significantly prolong the anaesthetic and analgesic effects of bupivacaine in

a dose dependent manner[10]. Hence, we used 75  $\mu$ g of clonidine in our study. We found that the onset of sensory blockade was accelerated with the addition of neostigmine, suggesting that neostigmine enhances action of spinally administered local anaesthetics. The mechanism behind this action might be due to neostigmine being an acetyl cholinesterase inhibitor, inhibits breakdown of the endogenous neurotransmitter acetylcholine, thereby inducing analgesia. Thus it can be used as an alternative non opioid additive to local anaesthetics without any opioid associated side effects[13].

Pan *et al* found that the onset of sensory block was rapid in neostigmine group than the clonidine group in caesarean patients[14]. We also found similar findings. Yoganarasimha *et al* also found similar findings of faster onset of sensory and motor block neostigmine when compared to clonidine[1].

We also found that the duration of analgesia was prolonged with the addition of clonidine when compared to that by neostigmine. The mechanism of action of clonidine is thought due to prolonging the motor blockade produced by local anaesthetic agents and also by bringing local vasoconstriction by acting on vascular smooth muscle ( $\alpha$ -receptors), thereby decreasing the absorption of local anaesthetics from sub-arachnoid space leading to an increase in the duration of action[15,16].

According to Liu *et al*, neostigmine increases spinal levels of acetylcholine, thereby augmenting motor

block[17]. Sethi BS *et al* showed that addition of clonidine to bupivacaine in the dose of 1 µg/kg significantly increased the duration of analgesia when compared to bupivacaine alone.<sup>7</sup> Gupta *et al* reported an enhanced analgesia by intrathecal neostigmine in 75 µg dose as they observed less consumption of intramuscular diclofenac sodium[18].

We found that 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 clonidine group. Our findings are in accordance with Klamt *et al*[19].

Studies have shown that intrathecal administration of neostigmine brings about acetylcholine-induced stimulation of preganglionic sympathetic neurons, thereby causing an increase in heart rate and blood pressure[20,21]. We found an increase in heart rate in patients receiving intrathecal neostigmine, similar to those observed by Klamt *et al*[19].

Studies have shown contradictory findings regarding blood pressure changes following various doses of intrathecal clonidine. Overall smaller doses of clonidine have shown to result in a fall in blood pressure by the effect on central brain stem nucleus and pre-ganglionic sympathetic inhibition. Whereas, larger doses have shown to maintain BP through its effects on peripheral vasculature[10,22]. We found an increase of hypotension following intrathecal administration of 75 µg of clonidine, but it could be easily managed with vasopressors.

Hood *et al* showed side effects of nausea and vomiting perioperatively after administration of intrathecal administration of neostigmine. According to them, this might be due to rostral spread of neostigmine to the brainstem site [21]. We did not notice any side effects in our patients. This might be due to dilution of drug with local anaesthetic. We suggest more such studies with larger sample size so as to establish the equipotent doses of these drugs.

## Conclusion

We carried our study to compare the effect of intrathecal clonidine 75 µg or neostigmine 50 µg added to intrathecal hyperbaric bupivacaine and found that neostigmine significantly hastened the onset of sensory and motor block without prolonging the duration of analgesia compared to clonidine.

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