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Intrathecal neostigmine with hyperbaric bupivacaine on the effects of spinal anaesthesia and postoperative analgesia – randomised prospective double blind study

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Abstract

Background and Aims: Postoperative analgesia after intrathecal bupivacaine is limited to a few hours. The aim of this study was to assess the effects of intrathecal Neostigmine added to hyperbaric bupivacaine on the onset and duration of spinal anaesthesia and in prolonging postoperative analgesia.

Methods: A prospective, randomized double blind study was conducted in 90 patients of ASA grades I and II, in three groups of 30 each, scheduled for lower limb surgeries under subarachnoid block. Patients in Group 1 received 0.5% hyperbaric Bupivacaine 2.5ml (12.5mg) + 0.1ml of sterile normal saline, Group 2 received 0.5% hyperbaric Bupivacaine 2.5ml (12.5mg) + 0.05ml Neostigmine (25μg) + 0.05 ml sterile normal saline and Group 3 received 0.5% hyperbaric Bupivacaine 2.5ml + 0.1ml Neostigmine (50μg). The onset and duration of sensory and motor block, time of two segment regression of sensory block, postoperative analgesia and side effects were studied.

Results: The mean onset time of sensory and motor block were comparable in the three groups. The sensory and motor block were prolonged by the addition of Neostigmine, of which adding 50μg Neostigmine was found to be statistically significant (p value <0.001). The visual analog scale (VAS) scores were significantly lower compared to control group upto 4 hours postoperatively in the 50μg Neostigmine group.

Conclusions: 50μg Neostigmine is needed to produce significant prolongation of analgesia without significantly increasing the adverse effects, and it reduces the VAS score and analgesic consumption postoperatively.

Keywords: Neostigmine, Bupivacaine, Spinal anaesthesia, Postoperative analgesia

Introduction

Intrathecal administration of various agents has been described to provide postoperative analgesia. Opioids have been used commonly but have the potential for adverse effects especially delayed respiratory depression.(1) In an attempt to develop non opioid analgesic with fewer adverse effects various other agents like α2 adrenergic agonists, gamma aminobutyric acid, N methyl-D-Aspartate antagonists, non-steroidal anti-inflammatory drugs, steroids and acetylcholinesterase (Ach E) inhibitors have been used.

The cholinergic system plays an important inhibitory pathway for pain modulation.(2,3) Postoperative analgesic effect of intrathecal Neostigmine was first reported by Hood DD, et al in 1995.(4) Dose ranging from 10μg to 200μg of Neostigmine had been studied in the recent past and shown to produce effective postoperative analgesia. They inhibit the breakdown of acetyl choline and thereby induce analgesia.(5) It also prolongs and intensifies the analgesic effect through release of nitric oxide in the spinal cord.(6,7)

It also found to increase the spinal preganglionic sympathetic nervous system activity with a resultant increase in blood pressure. This vasopressor effect appears to be mediated by muscarinic receptor and has been shown to prevent the hypotensive effect of spinal block.(8,9) Autoradiographic studies have revealed the presence of muscarinic binding sites in the dorsal horn.(10,11) In the present study, we have compared the dose dependent effects of adding Neostigmine with hyperbaric bupivacaine on the characteristics of subarachnoid block in lower limb surgeries.

Methods

After Institutional Ethics Committee approval, a double-blind, prospective, randomized study was carried out over a period of one year on 90 patients in the age group of 18-60 years and ASA grades I and II undergoing elective lower limb orthopaedic surgeries. Patients with coagulation disorders, peripheral vascular disease, allergy to study drugs, mentally retarded patients, infection at the site of spinal injection were excluded. At pre-operative visit, the visual analog scale (VAS) scoring system was explained along with the nature and safety of the procedure. Written, valid, informed consent was obtained.

The patients were randomly recruited to 3 groups of 30 each using a computer generated random number list. The observers and the patients were blinded to the group the patients belonged to. This was done to achieve allocation concealment. Patients in Group 1 (control) received 0.5% hyperbaric bupivacaine 2.5ml (12.5mg) + 0.1ml sterile normal saline, Group 2 (N_{25})

received 0.5% hyperbaric bupivacaine 2.5ml + 25μg (0.05ml Preservative-free Neostigmine) + 0.05ml sterile normal saline. Group 3 (N_{50}) received 0.5% hyperbaric bupivacaine 2.5ml + 50μg (0.1ml Preservative-free Neostigmine). Neostigmine was measured with the help of insulin syringe and mixed with the Bupivacaine.

After preanaesthetic checkup, all patients received Tab Ranitidine 150mg and Tab Alprazolam 0.5mg at bed time. After 8hours of fasting, Tab Ranitidine 150mg, Tab Ondansetron 8mg and Tab. Domperidone 10mg were given 2 hours prior to surgery with sips of water. On arrival to the operation theatre, monitoring was done for pulse rate, noninvasive blood pressure, respiratory rate, ECG and SPO_2. Intravenous line was established after local anaesthetic infiltration with 0.5% Lignocane and infusion was started with normal saline. All patients received 4mg Ondansetron intravenously prior to anaesthesia as a study protocol. Under strict asepsis spinal anaesthesia was done with 25G Quinke needle in L3-4 space. After obtaining clear free flow of CSF, injection Bupivacaine alone or in combination with Neostigmine was administered depending upon the group studied. All patients received oxygen (5L/minute) throughout the procedure as an institutional protocol.

Patient data were recorded by an observer blinded to the treatment group. Blood pressure, heart rate, respiration rate and oxygen saturation were recorded 5 minutes before the intrathecal injection, at 2 minutes interval for the first 10 minutes, at 5 minutes interval for next 20 minutes and then every 10 minutes for 2 hours or until block worn off, whichever was earlier.

The parameters studied were onset of sensory block (checked at 30 seconds interval with 23 gauge needle prick at T10 dermatome), maximum level of sensory blockade (sensory level noted at 2 minute interval till 3 consecutive level seen to be the same with no further rise), motor block assessed by modified Bromage scale, duration of motor block (time of regression of motor blockade to Bromage scale grade 0 checked and recorded every 15 minutes after completion of surgery), time of two – segment regression of sensory blockade and postoperative assessment for the variables such as pain score by Visual Analog Scale (VAS) and duration of analgesia measured at hourly interval till four hours, 2 hourly for next six hours and then at 24 hours. Patients with VAS above 4 received rescue analgesia with Tramadol 50mg intramuscularly. These patients received additional antiemetic prophylaxis with Inj.Ondansetron 4mg. intravenously 12th hourly for 24hours. Total analgesic requirement during 24h period was also recorded. Side effects like nausea, vomiting, increased salivation, shivering, urinary retention, sedation and pruritus were assessed. Fluid balance, usage of vasopressors and atropine were recorded.

Data were analysed using computer software, statistical package for social science (SPSS) version 10. Data were expressed in its frequency and percentage. Quantitative variables were compared with analysis of variance (one way ANOVA). Qualitative variables were compared with Chi square test. P value of <0.05 was taken as significant.

Results

All the groups were statistically comparable with respect to age, sex, weight and duration of surgery (Table 1).

Table 1: Demographic data of patients

Parameters	Groups		
Control	N25	N50	
Age (Years)*	34.5 (7.718)	32.37 (8.536)	36.60 (9.194)
Height (cm)	158.37 (6.245)	162.97 (7.285)	164.63 (8.389)
Weight (kg)	54.65 (5.46)	56.00 (5.73)	58.35 (7.49)
+Sex Ratio (M:F)	20:10	20:10	22:8
Duration of surgery (min)	58.70 (18.549)	47.73 (11.779)	56.73 (16.171)

Values expressed as mean(Standard Deviation)

The mean onset of sensory and motor block were comparable in all the three groups (Table 2). However, two sensory dermatome regression time of sensory block was prolonged in a dose dependent manner by the addition of Neostigmine of which prolongation by the addition of 50μg Neostigmine was found to be statistically significant (Table 3).

Table 2: Onset of Sensory and Motor block

Group	Onset of Sensory Block (min)		Onset of Motor Block (min)	
	Mean	SD	Mean	SD
Control	3.77	1.654	4.10	1.709
N25	3.97	1.299	4.43	1.165
N50	3.87	0.9	4.60	1.694
P value (ANOVA)			P value (ANOVA)	
C vs N25	1.00		1.00	
C vs N50	1.00		0.639	
N25 vs N50	1.00		1.00	

Table 3: Comparison of two sensory dermatome regression time

Group	Two segment regression time (min)	
	Mean	SD
Control	98.5	16
N25	104	15
N50	119	14
P value (ANOVA)		
C vs N25	0.506	
C vs N50	0.001	
N25 vs N50	0.001	

The duration of motor block was assessed by the return of modified Bromage scale to zero. It was prolonged by the addition of Neostigmine and found to be dose dependent. Prolongation of motor block was found to be statistically significant in the 50 μg Neostigmine group (Table 4).

Table 4: Comparison of duration of motor block

Group	Duration of motor block (min)	
	Mean	SD
Control	169.33	22.959
N25	181.50	15.928
N50	199.50	21.268
P value (ANOVA)		
C vs N25	0.067	
C vs N50	<0.001	
N25 vs N50	0.003	

Intraoperative fluctuations in blood pressure and heart rate were managed with fluids, vasopressors and atropine. The hemodynamic variables and the usage of vasopressors did not show any significant correlation with the dosage of Neostigmine.

Regarding postoperative analgesia, the VAS scores in the test groups (N25 and N50) were significantly lower compared to control group upto 4 hours postoperatively, beyond that no meaningful difference was found to exist among the groups. Total VAS scores in 24 hours in the groups were also compared. 25μg Neostigmine group did not show significant difference, however 50μg Neostigmine showed significant decrease in total VAS scores (Table 5).

Table 5: VAS score at different time interval and Total VAS score at 24hrs

Group	1hr	2hrs	3hrs	4hrs	6hrs	8hrs	10hrs	24hrs	Total
Control	0	0.1±0.305	1.73±0.640	2.87±0.507	3.07±0.828	3.13±0.819	3.00±0.830	3.07±0.640	21.5±1.7
N25	0	0.05±0.305	1.33±0.479	2.30±0.596	3.10±0.712	3.50±0.731	3.40±0.621	2.43±0.568	19.50±1.76
N50	0	0.07±0.254	1.13±0.346	2.27±0.450	3.00±0.528	2.80±0.761	2.63±0.490	2.70±0.77	13.85±4.01
P value									
Control vs N25		0.001	0.008	<0.001	1.00	0.207	0.065	0.002	0.151
Control vs N50		<0.001	<0.001	<0.001	1.00	0.293	0.104	0.143	0.001
N25 vs N50		0.001	0.381	1.00	1.00	0.002	<0.001	0.44	0.001

On observation it was found that Neostigmine produced a dose dependent increase in mean duration of analgesia. While 25μg Neostigmine failed to produce a statistically significant increase in the duration of analgesia, 50μ Neostigmine did significantly prolong the duration of analgesia (Table 6).

Analgesic consumption in 24 hours was also compared among the groups. We observed a significant decrease in the total analgesic consumption in the 50μg Neostigmine group (Table 6).

Table 6: Comparison of total duration of analgesia and analgesic consumption

Group	Total duration of Analgesia (min)		Analgesics Used	
	Mean	SD	Mean	SD
Control	230.07	55.037	2.70	0.596
N25	258.53	41.995	2.47	0.571
N50	288.17	66.895	1.97	0.490
P value (ANOVA)			P value (ANOVA)	
C vs N25	0.151		0.32	
C vs N50	<0.001		<0.001	
N25 vs N50	0.126		0.002	

The side effects studied were nausea, vomiting, shivering, hypotension, bradycardia, respiratory depression and pruritus. There was no statistically significant difference in the incidence of side effects among the three groups. An increase in incidence of nausea and vomiting were observed in the two test groups. Two patients in the N25 group and five in the N50 group complained of nausea while one in N25 and three in N50 had vomiting. However, on analysis this was found to be statistically not significant (p value >0.05).

Discussion

Subarachnoid block is the most commonly used anaesthetic technique for the lower limb orthopaedic surgeries because of its simplicity, rapid onset, intense analgesia, decreased intraoperative blood loss and the relatively less postoperative anaesthetic complication.[12]

In our study we selected 90 patients undergoing lower limb surgeries. Selection bias was minimized by randomization. The number of patients was enough to set a significant outcome. Most of the patients were healthy other than their orthopaedic problem and were young and educated with mean age ranging from 32 to 36, which made assessment of postoperative variables more reliable. We selected orthopaedic surgeries of short and comparable duration which made our analysis of postoperative variables more uniform and precise and also excluded the patients and surgeries which predispose to emesis, hypotension and bradycardia. Most of the studies on Intrathecal Neostigmine reveal high incidence of nausea and vomiting which limit its clinical utility. So to reduce this, all patients in our study were given antiemetic prophylaxis with Inj.Ondansetron 4mg. IV prior to subarachnoid block as a study protocol.

The intrathecal Neostigmine we used was preservative-free. Several studies documented the negative side effects of injecting preservative containing drugs into the intrathecal and epidural spaces such as arachnoiditis, sterile meningitis, pachymeningitis and other adverse neurological events. So it is the accepted practice that intrathecal injections should be preservative-free.

Intrathecal Neostigmine causes motor block by an Acetyl choline mediated reduction in motor neuron outflow with no reduction in spinal cord blood flow or histopathological changes. In addition, increased spinal levels of acetylcholine may augment motor blockade of spinal bupivacaine.

Tan, et al and Liu, et al observed that intrathecal Neostigmine enhanced the onset of sensory block[13] but in our study the onset of sensory blockade was comparable among groups. Liu, et al had shown that Neostigmine 50μg when added to low dose bupivacaine prolonged the duration of sensory block.[14] The authors explained the enhancement of onset of sensory block and its prolongation to be due to the intrinsic analgesic efficacy of intrathecal Neostigmine. Our result corroborates with the above mentioned study.

Onset of motor block was similar in all groups (p value >0.05). Chung, et al,[15] also observed no significant enhancement of onset of motor block by the addition of Neostigmine. The duration of motor block was found significantly prolonged with the addition of 50μg Neostigmine. Liu, et al. also observed similar prolongation of motor block with addition of 50 μg Neostigmine. This prolongation of motor blockade is an undesirable side effect, especially for short duration surgeries and day-care procedures.

Regarding postoperative analgesia, Chung et al[15] and Lauretti, et al[16] observed statistically significant lower VAS score in the dose ranging from 25 to 75μg Neostigmine group compared to the control. We found significant postoperative analgesia in the 50μg Neostigmine group. The role of intrathecal Neostigmine added to bupivacane in enhancing the total duration of analgesia including postoperative analgesia is well documented. The only deterrent in using this combination had been the high incidence of postoperative nausea and vomiting as reported by Spencer S Liu, et al,[17] Hood, et al[4] and Klamt, et al.[17] In our study we could significantly reduce nausea and vomiting by proper antiemetic prophylaxis. But out of thirty patients, five patients in the 50μg Neostigmine group developed nausea (16.6%), and three patients vomited clear gastric content (10%). On chi-square analysis the incidence was found to be statistically insignificant (p value >0.05). Intrathecal Neostigmine produces nausea in a dose dependent manner. This high incidence of nausea and vomiting could possibly be due to cephalad migration of Neostigmine to the brain stem. At brain stem, Neostigmine causes accumulation of acetyl choline to act on the chemoreceptor trigger zone which induces vomiting. We did not observe any significant incidence of other side effects such as respiratory depression, sedation, pruritus, in the test groups.

Conclusion

Intrathecal administration of Neostigmine along with hyperbaric bupivacaine produces significant prolongation of spinal anaesthesia and postoperative analgesia. However, 50μg is needed to produce significant prolongation of analgesia without increasing the adverse effects. It also reduced the postoperative VAS score and analgesic consumption. However, effort must be made to reduce nausea and vomiting by adequate antiemetic prophylaxis for Neostigmine to be clinically useful. So we recommend the clinical use of intrathecal Neostigmine at a minimum dose of 50μg along with adequate antiemetics.

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Conflicts of interest

There are no conflicts of interest

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