



Original Research Article

Comparison of two different doses of intrathecal Neostigmine as an adjuvant to Bupivacaine for postoperative analgesia

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ABSTRACT

Background and Aims: Subarachnoid block (SAB) using Bupivacaine lacks postoperative analgesia. Aim of present study was to assess safety and efficacy of 50 μ and 100 μ intrathecal Neostigmine for postoperative analgesia.

Materials and Methods: Ninety patients of age 18 to 65 were allocated randomly to three groups of 30 each and studied prospectively by double blind controlled trial. Patient posted for lower limb and lower abdominal surgeries were given SAB using 3 ml Bupivacaine 0.5% in group A, 2.9 ml Bupivacaine + 50 μ Neostigmine in B and 2.8 ml Bupivacaine and 100 μ Neostigmine in C.

Patients were monitored for onset, regression of sensory and motor block, blood pressure and heart rate. Postoperatively patients were assessed for pain score using visual analogue scale (VAS) and duration of analgesia by rescue analgesia requirement.

Results: 90 patients enrolled were analysed. VAS pain score was more in group A compared to B which had higher than group C. Analgesia was prolonged in group C than in B which had better analgesia than group A. Incidence of nausea, vomiting and bradycardia was higher with 100 μ Neostigmine than 50 μ .

Conclusion: Intrathecal Neostigmine 50 μ dose as an adjuvant to Bupivacaine is associated with good postoperative analgesia and hemodynamic stability while 100 μ dose was associated with more prolonged analgesia and higher incidence of adverse effects.

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1. Introduction

Subarachnoid block using Bupivacaine has been widely practiced worldwide. Perioperative hemodynamic instability and lack of postoperative analgesia for longer duration remains important issues with it, for which many additives have been tried with various efficacy and side effects. Neostigmine, one of the additive, when used intrathecally, prevents breakdown of acetylcholine which has antinociceptive effect by direct effect on spinal cholinergic M1 and M3 Muscarinic receptor and subtypes of nicotinic receptor, as well as secondarily by stimulating release of nitric oxide in the spinal cord as a second messenger.¹⁻⁴ Intrathecal Neostigmine does not

lead to respiratory depression, hypotension, sedation or neurological adverse effects as with other additives.⁵ In present study we aimed to compare 50 μ g and 100 μ g doses of Neostigmine administered intrathecally as an additive along with Bupivacaine for postoperative analgesia and associated adverse consequences and its effect on hemodynamics.

2. Materials and Methods

Approval was obtained from institutional ethics committee. A well informed and written consent was taken from 90 patients of age group 18 to 65 years, grade I and II of American Society of Anesthesiologists posted for lower limb orthopedic procedures and for lower abdominal procedures viz. inguinal hernia repair and appendectomy under subarachnoid block.

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Random allocation of patients into three groups of 30 patients each was done. Visual analog scale for pain was explained in which zero suggest pain free patient and 10 denotes worst possible pain was explained to the patients preoperatively.

After taking patient in operation theatre, standard monitors were attached including electrocardiogram, noninvasive blood pressure and pulesoxymeter probe. Premedication was done using Pantoprazole 40mg intravenously. Patient was preloaded with 5 ml/ kg of Ringer's lactate solution 15 minutes prior to spinal anaesthesia (SA). A total 3 ml of volume was injected using 25 G spinal needle at of 0.2 ml/ second rate with patient placed on one side. Group A received 3 ml of 0.5% of Bupivacaine heavy, Group B was given 2.9 ml Bupivacaine with 0.1 ml of Neostigmine i.e. 50 μ while group C was injected with 2.8 ml Bupivacaine heavy with 0.2 ml (100 μ) of Neostigmine. Patients were turned supine immediately after intrathecal injection. Separate Anesthesiologists one for preparation and administration of intrathecal drug and other for intraoperative and postoperative monitoring were assigned.

Pinprick test was used to assess sensory loss after 5, 10, 15 and 20 minutes following injection of drug to be studied intrathecally and thereafter every 30 minutes, till the conclusion of surgery. Modified Bromage scale was used intraoperatively every 5 min for the first 20 minutes to assess motor block. Heart rate, blood pressure and saturation of oxyhemoglobin were observed every 5 minutes all over the procedure. Fall in mean arterial pressure below 60 mm of Hg or by 25% of preoperative value was treated with Mephentermine 6 mg in incremental dose. Fall in heart rate less than 50 per minute or 15% below baseline was considered bradycardia and 0.6 mg of Atropine IV was used for its treatment.

Postoperatively patients were assessed for pain scores using VAS score (10 point scale) recorded at hourly interval for first four hours, then two hourly for next six hours and thereafter at 24 hours. Patients were also looked for postoperative nausea and vomiting, respiratory depression and any other significant complications. Patients were followed up till 24 hours and time for first dose of rescue analgesia which was given using Inj Diclofenac 1.5 mg/kg was reported. Patient's request for the rescue analgesia or score of more than three on VAS pain scale whichever comes first was considered as duration of effective analgesia. Nausea and vomiting was recorded using five point scale and one or more episode of vomiting was treated with intravenous Ondansetron 4 mg.

One-way analysis of variance was used to compare Demographic data and surgical duration. Heart rate, blood pressure, highest level and time to achieve highest level of sensory blockade as well as total motor blockade, and pain scores on VAS scale were compared in three groups using

two-way analysis of variance and then by Mann–Whitney test. $P < 0.05$ was considered significant. The effective analgesia duration and total number of patient requiring rescue analgesia within 24hours was compared using Kruskal–Wallis test, applied along with Mann–Whitney test. $P < 0.05$ was considered significant. Data analysis was done with STATA version 14.0 of statistical software.

3. Results

Study had enrolled 90 patients. Demographical characters including age, sex, weight, height and surgical duration were comparable. ($p > 0.05$). (Table 1)

With increasing dose of Neostigmine attainment of sensory blockade was faster and regression of sensory block was i.e. time taken to recede to L1 level was markedly higher with increased dose of Neostigmine in group C than in group B which was also higher compared to group A (Bupivacaine only). Maximum sensory level achieved was also greater in group C compared to group B which had higher level than group A (Table 2).

Onset of motor blockade was faster with Neostigmine group and higher dose had even more rapid onset. It can also be seen that motor block regressed rapidly in group A as compared to group B which had earlier regression than group C (Table 3).

It shows that the pulse rate has significantly declined from baseline in Neostigmine Groups i.e. B and C group than in Group A at initial 30 minutes interval.

It has been observed that Systolic Blood Pressure (SBP) is significantly decreased from baseline in Group A whereas no significant drop in SBP is seen in Group B and Group C

It has been observed that MAP is significantly decreased from baseline in Group A whereas no significant drop in MAP is seen in Group B and Group C.

VAS score at 1st hour postoperative was taken as baseline and change in VAS score was noted at different time intervals (Graph 4). It has been observed that increase in VAS score is earlier in Group A as early as 3 hours followed by Group B around 5 hours and then Group C around 8 hours which signify that analgesia duration is remarkably increased in Group C > Group B > Group A as shown in Graph 4.

The time required for first rescue analgesia in Group C was significantly longer that Group B which was again longer as compared to Group A as shown in Table 4.

Incidence of bradycardia and so also nausea and vomiting was remarkably higher in group c than in group B which also had more incidence than group A while hypotension was more in group A.

4. Discussion

Antinociceptive effects of intrathecal Neostigmine is mediated by Muscarinic receptors in the spinal cord.

Table 1: Demographic data of patients

Parameters	Group A	Group B	Group C	P-value
Mean age (years)	37.23 ± 11.52	36.4 ± 10.58	40.53 ± 11.25	0.3169(NS)
Mean Height(cm)	157.53 ± 4.17	158.5 ± 5.43	162.73 ± 5.31	0.002(HS)
Mean Weight (kg)	55.46 ± 5.93	55.2 ± 5.46	57.96 ± 7.80	0.1952(NS)
Gender (male :female)	23: 7	22:8	15:15	0.059(NS)
Mean Duration of surgery (minutes)	99.83 ± 18.54	97.16 ± 17.10	89.83 ± 17.78	0.0853(NS)

Table 2: Characteristics of spinal sensory block

Parameters	Group A	Group B	Group C	P-value
sensory block mean onset time (sec)	87.46 ± 17.47	70.73 ± 12.21	44.83 ± 17.66	<0.0001, HS
Mean maximum sensory level (T 4 - T 10)	7.26 ± 1.43	7.13 ± 1.35	6.33 ± 1.18	0.0163,S
Mean time to achieve Maximum sensory level (min)	6.7 ± 0.91	6.1 ± 0.76	5.29 ± 0.62	<0.0001,HS
Time to regress to L1 level (min)	161 ± 8.34	176.5 ± 8.92	185.67 ± 6.78	<0.0001, HS

Table 3: Characteristics of motor block

Parameters	Group A	Group B	Group C	P- value
time to achieve MBS 2 (minute)	5.7 ± 1.34	5.26 ± 0.98	4.6 ± 0.56	0.0003, HS
time to regress to MBS 0	143 ± 6.89	195.67 ± 14.66	278.33 ± 9.49	<0.0001, HS

Table 4: Mean time required for First dose of rescue Analgesia

Observation	Group A	Group B	Group C	P-value
Mean duration of first dose of rescue Analgesia (min)	183.33 ± 10.61	232.83 ± 15.01	300.16 ± 10.94	<0.0001, HS

Table 5: Intraoperative and postoperative complications

Complications	Group A	Group B	Group C	P value
Bradycardia	0	6	8	0.012,S
Nausea / vomiting	2	2	7	0.045,S
Hypotension	9	3	2	0.026,S
Respiratory depression	0	0	0	1,NS

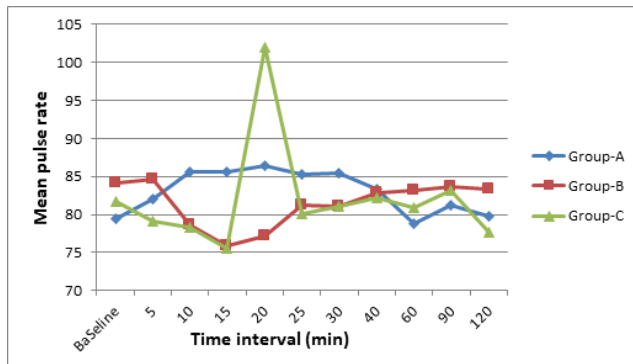
Analgesia is produced by inhibiting the metabolism of acetyl choline which acts on Muscarinic binding sites in substantia gelatinosa and lamina III and V of spinal grey matter causing antinociception.⁶ In present study we aimed to compare two dose of Neostigmine in terms of their analgesic efficacy, hemodynamic stability and incidence of adverse effects. Doses of 50 and 100 μ were selected based on previous study by Liu et al⁷ and Vandana Pandey et al.⁸

Onset time of sensory as well as motor blockade was faster in group B and group C than in group A Amongst three groups, group C has fastest onset of sensory block, showing that Neostigmine enhances action of spinally administered local anaesthetics. Also mean time to achieve

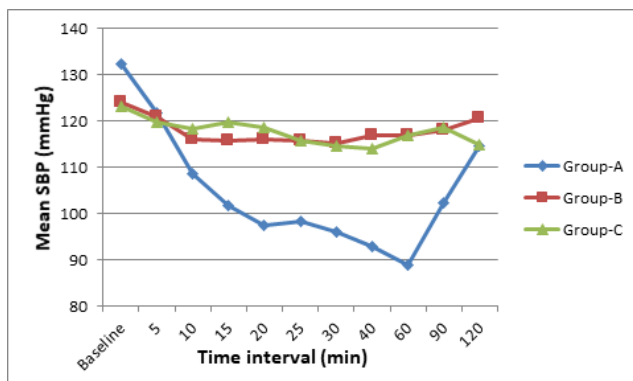
maximum sensory block was earlier in group C followed by group B and then group A. This finding was similar to study by Yoganarasimha N et al.⁹

Time taken to regress block to L1 was significantly slower in C group than group B while group A had earlier regression than previous two. These findings were consistent with previous studies by Liu et al.⁷ and Pan et al.¹⁰

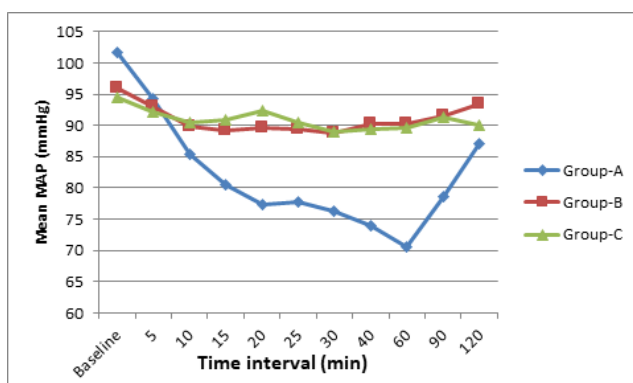
Our study found that 100 mcg of intrathecal Neostigmine had more prolonged duration of analgesia lasting up to 8 hours as compared to 50mcg dose which lasted around 5hours which was better than when Bupivacaine was used alone around 3 hours as demonstrated by total VAS score



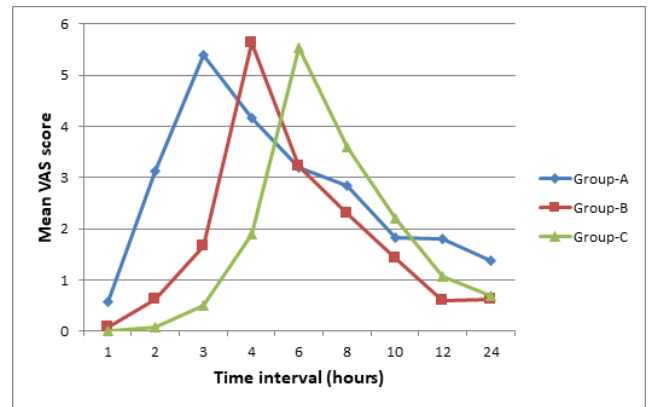
Graph 1: Intraoperative mean Pulse rate at different interval of time



Graph 2: Intraoperative Mean Systolic blood pressure at different interval of time



Graph 3: Intraoperative Mean arterial blood pressure at different interval of time



Graph 4: Postoperative Mean VAS score at different time interval

and time required for first dose of rescue analgesia. Time for first dose of rescue analgesia in group A was 183.33 ± 10.61 , in group B it was $232.83 \pm$ while in group C it was 300.16 ± 10.94 . All this findings were in concordance with studies by Lauretti et al.,¹¹ Krukowski et al.¹² Dr Yognarsimha et al.⁹ and S. Gupta et al.¹³

In our study we found that systolic as well as mean arterial pressure was well maintained in both Neostigmine group i.e. B and C while group A had fall in systolic as well as mean arterial pressures. These findings were in concordance with the study by Hye Ma et al. and Carp Het al.^{14,15}

We found that group C had higher incidence of bradycardia in than in group B while group A had no incidence of bradycardia. Also we found that nausea and vomiting was remarkably higher in C group than in group B and group A. Craniad relocation of Neostigmine at brain stem due to higher dose of it results in accumulation of acetyl choline at brain stem causing stimulation of chemoreceptor trigger zone resulting in higher incidence of nausea and vomiting. Tan et al.¹⁶ also found similar results in their study. None of the patients in our study had episode of oxyhemoglobin desaturation, increased salivation or ejaculation, findings consistent with study of Chung et al.¹⁷

5. Conclusion

Intrathecal Neostigmine, an adjuvant, when used with Bupivacaine gives hemodynamically stable and prolonged period of postoperative analgesia than Bupivacaine only. Dose of 100μ of Neostigmine was associated with better VAS score and decreased consumption of rescue analgesic but with higher incidence of bradycardia and nausea and vomiting. While dose of 50μ also provided prolonged postoperative analgesia and lesser incidences of side effects like nausea, vomiting and bradycardia so it can be used for low cost, opioid free spinal anaesthesia without risk of hemodynamic instability or respiratory depression.

6. Source of Funding

Nil.

7. Conflicts of Interest

Nil.

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