

EVALUATION OF INTRATHECAL NEOSTIGMINE IN DIFFERENT DOSES ADDED TO BUPIVACAINE FOR POSTOPERATIVE ANALGESIA

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Background: Neuraxial administration of neostigmine alongwith local anaesthetics improves the quality of intraoperative analgesia and also provides postoperative pain relief for longer duration. The present study was conducted to study the efficacy and safety of intrathecal neostigmine with bupivacaine in two different doses.

Methods: Ninety patients of ASA I and II undergoing lower abdominal and lower limb surgeries under spinal anaesthesia were enrolled and divided into 3 groups of 30 each. Group A: bupivacaine control group, Group B: bupivacaine plus 50mcg neostigmine and Group C; bupivacaine plus 150mcg neostigmine. Haemodynamic parameters, sensory and motor characteristics along with side effects were recorded. The post operative pain assessment was done by visual analogue scale score at hourly intervals for the first four hours, then two hourly intervals for the next 6 hours and thereafter at 24 hours. It was scaled from a score of 0 meaning no pain to a score of 100 meaning worst pain perceived. Time of two segment regression of sensory blockade and total duration of motor block was significantly prolonged in group B and C as compared to the control group.

Results: The mean total duration for analgesia was significantly prolonged in Group B (340±8.36) and Group C (700±8.65) when compared to group A (263.30±7.57) (p<0.05).

Conclusion: We conclude that intrathecal neostigmine results in effective postoperative analgesia prolonging sensory and motor block without hemodynamic and respiratory depression in the intra and postoperative period.

International Association for the study of Pain defined pain as an “unpleasant sensation and an emotionally charged experience associated with actual or potential tissue damage or described in terms of such damage”¹. Because of concern over intra spinal opioid induced side effects other drugs have also been examined for spinal analgesia, notably α_2 agonists like clonidine, N methyl D aspartate (NMDA) antagonists like ketamine and anticholinesterases like neostigmine. Intrathecal neostigmine represents a novel approach to provide analgesia. It inhibits the breakdown of an endogenous spinal neurotransmitter acetylcholine which has been shown to have antinociceptive actions. Acetylcholine released from preganglionic sympathetic ganglia has been shown to have action at other spinal sites like inhibition of motor neuron activity, excitation of sympathetic

outflow.² Spinal neostigmine is advantageous over other currently used spinal drugs as it causes no hypotension (excitation of sympathetic outflow), no sedation, no respiratory depression or neurological dysfunction.^{2,3} Bupivacaine was the first local anaesthetic that produced adequate pain relief, without a major effect on motor fibres.⁴ Neostigmine has been shown to counteract haemodynamic effects of clonidine and bupivacaine.^{5,6} Considering the above facts, we designed the present study to evaluate efficacy and safety of intrathecal bupivacaine alone and in combination with neostigmine for postoperative analgesia.

Materials and Methods

After Institutional Ethics Committee clearance and written informed consent from patients,

ninety patients undergoing lower abdominal and lower limb surgeries under spinal anaesthesia participated in the study. The patients were in the age group of 20 to 40 years of both sexes and belonging to ASA physical status Grade I and II. Following patients were excluded from the study: Unconscious or mentally retarded, drug addicts, weight > 100kg, bleeding disorders or on anticoagulant therapy, known allergy to the study drugs and local infection at the site of injection. In the preoperative visit on the evening before surgery, the method of postoperative pain scoring was explained and a training given to all patients.

The patients were randomly allocated to three groups:-

Group A(n=30) received 2.5ml intrathecal bupivacaine 0.5% (Control group)

Group B (n=30) received 50µg intrathecal neostigmine + 2.5 ml bupivacaine 0.5%

Group C(n=30) received 150µg intrathecal neostigmine + 2.5 ml bupivacaine 0.5%

Neostigmine was measured and taken to an insulin syringe and mixed with bupivacaine. The observer was blinded to the group the patient belonged to.

Preanesthetic checkup of all the patients was done prior to the day of surgery. Patients were kept fasting for 8 hours prior to the surgery and received tablet ranitidine 150mg at bed time and 2 hours preoperatively as premedication with a sip of water. On arrival in the operation theatre heart rate (ECG), blood pressure (NIBP), respiratory rate, and arterial O₂ saturation(SaO₂) were monitored. An infusion of normal saline was started in all patients and preloaded with 10ml/kg of normal saline. Patients were placed in lateral or sitting position according to their convenience. Lumbar puncture was performed with 23 or 25 gauge Quincke's needle in L₂L₃ or L₃L₄ intervertebral space. After obtaining free flow of clear cerebrospinal fluid, bupivacaine alone or in combination with neostigmine was administered depending upon the group. Patients were immediately turned supine after administration of subarachnoid block. All patients received 2l/min oxygen throughout the surgical procedure. Level of sensory block was determined using the pin prick method. Motor block was assessed by Bromage scale:
Grade III inability to move leg or feet
Grade II able to move feet only

Grade I just able to flex knees and full flexion of feet possible

Grade 0 full flexion of knee and feet, able to lift leg

Time from start of anaesthesia to Bromage grade II was noted. Time of 2 segment regression of sensory blockade and time of motor blockade to Bromage Grade 0 was checked and recorded every 15 minutes after completion of surgery. Intraoperative haemodynamic stability was ensured. Post operative pain assessment was done by visual analogue scale score at hourly intervals for the first four hours, then two hourly for the next 6 hours and thereafter at 24 hours. It was scaled from a score of 0 meaning no pain to a score of 100 meaning worst pain perceived. Patients with VAS above 40 received rescue analgesia in the form of injection diclofenac sodium 75 mg i/m. Time to analgesic dose required in the postoperative period and VAS score was assessed. Occurrence of nausea, vomiting, increased salivation, sweating, sedation, hypotension and bradycardia were noted. The patients were given injection Ondansetron 4mg i/v for nausea and vomiting. Statistical analysis was done by SPSS 2 software using ANOVA and chi square. A p value of <0.05 was considered statistically significant.

Results

Three groups were comparable with respect to age, weight, baseline SpO₂, blood pressure and heart rate.

An adequate surgical block was documented before start of surgery and the time taken to reach this level was comparable between the three groups. Although there was no significant difference in the onset of sensory block and height of maximum sensory blockage between the three groups as shown in table 3.

Table 1 Comparison of mean values of age and weight in the 3 groups

Group	Age	Mean±SD	p	Wt.	Mean±SD	p	Comparison
A n30	22 - 36	28.43± 3.84	0.1385	56 - 68	62.10± 2.89	>0.05	A vs B
B n30	21 - 36	26.90± 4.05	0.8113	57 - 67	62.23± 2.76	>0.05	B vs C
C n30	22 - 35	27.13± 3.32	0.1668	57 - 69	62.37± 2.91	>0.05	A vs C

Fig. 1 Mean heart rate variations in the three groups.

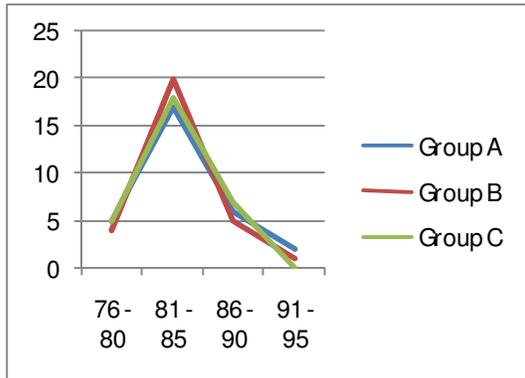


Table 2 Comparison of mean SpO₂ of the three groups

SpO ₂	Group	Range	Mean	SD	p value	Significance	Comparison
Before Spinal Anesthesia	A	92 - 99	95.43	1.98	>0.05	NS	A vs B
	B	92 - 98	95.03	1.96	>0.05	NS	B vs C
	C	92 - 99	95.37	2.03	>0.05	NS	A vs C
Lowest Recorded	A	93 - 99	97.37	1.54	>0.05	NS	A vs B
	B	94 - 99	96.70	1.49	>0.05	NS	B vs C
	C	94 - 99	97.03	1.59	>0.05	NS	A vs C

Onset of sensory block had a mean \pm S.D. value of 4.417 ± 0.439 , 4.403 ± 0.432 and 4.437 ± 0.437 min respectively for groups A,B and C respectively but on comparing the time to 2 segment regression we obtained values of 115.23 ± 2.73 , 127.60 ± 6.03 and 140.67 ± 4.54 respectively for groups A,B and C which were statistically significant on comparison. Onset of motor block was comparable and statistically there was no significant difference between the three groups ($p>0.05$). However duration of motor block was 189.83 ± 5.64 , 197.00 ± 7.01 and 220.30 ± 9.70 min for groups A, B and C respectively, $p < 0.05$ on comparison.

Table 3 Spinal block Characteristics (mean \pm SD)

	A	B	C	p	Significance
Time to sensory block to T4 (min)	4.417 ± 0.43	4.403 ± 0.432	4.437 ± 0.437	>0.05	NS
Time to complete motor block (min)	4.75 ± 0.503	4.770 ± 0.199	4.787 ± 0.178	>0.05	NS
Time taken for sensory regression to T12 (min)	115.23 ± 2.73	127.60 ± 6.03	140.67 ± 4.54	<0.05	S
Time to complete regression of motor block (Bromage 0)	189.83 ± 5.64	197.00 ± 7.01	220.30 ± 9.70	<0.05	S
Time from injection to 1 st dose of supplemental analgesia (min)	263.30 ± 7.57	340.10 ± 8.36	700.00 ± 8.65	<0.05	S

Figure 2 Incidence of various side effects in different groups

Nausea was observed in 4 patients in group B and 5 patients in group C. Vomiting was noted in 7 patients in group B and 11 patients in group C.

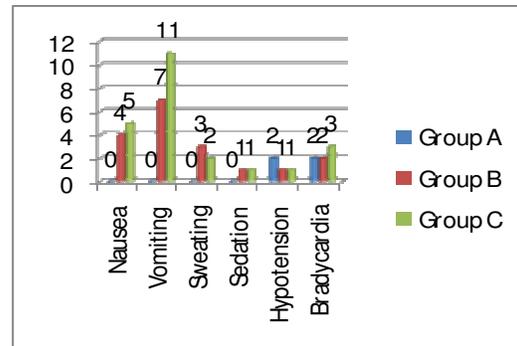


Table 4: VAS score at different postoperative time intervals in three groups

VAS	Time (hrs)po stop	1	2	3	4	6	8	10	12
Group	A	0	6.2±0.92	20.33±1.30	35.07±1.86	34.77±1.43	30.73±1.23	28.03±1.9	32.57±1.98
	B	0	1.50±0.82	11.93±1.46	25.2±1.56	32.50±1.81	26.13±2.13	28.17±1.97	32.47±1.92
	C	0	0.07±0.25	1.97±0.07	6±1.29	12.27±1.31	20.4±1.57	23.03±1.54	34±1.82
p value	A vs B	-	<0.05	<0.05	<0.05	<0.05	<0.05	>0.05	>0.05
	B vs C	-	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	>0.05
	A vs C	-	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	>0.05
Significance	A vs B	-	S	S	S	S	S	NS	NS
	B vs C	-	S	S	S	S	S	S	NS
	A vs C	-	S	S	S	S	S	S	S

VAS at 1 hr, 2hr, 3hr, 4hr, 6hr, 8hr, 10hr, 12hr & 24 hr in control group were higher and statistically significant (p<0.05) as compared to 50µg neostigmine (p<0.05) and 150 µg neostigmine groups (p<0.05).

Discussion

The word “pain” is derived from Latin word “poena” meaning punishment. Pain is the most frequent and perhaps the oldest symptom. Pain is always subjective and is unique among all senses because it has a strong emotional component along with the sensory component.⁷ Recent research has revealed spinal cholinergic pathways and transmitters involved in antinociceptive processing. Intrathecal

neostigmine, the cholinergic agent (a cholinesterase inhibitor) causes analgesia in humans.⁸ Acetylcholine being released from preganglionic sympathetic ganglia has been shown to have action at other spinal sites like inhibition of motor neuron activity and excitation of sympathetic outflow.² Spinal neostigmine is advantageous over other currently used spinal drugs as it causes no hypotension (excitation of sympathetic outflow), no sedation, no respiratory depression or neurological dysfunction.^{2,3}

In our study the mean lowest heart rate during spinal anaesthesia in all the three groups were comparable and statistically insignificant. On comparing the haemodynamic parameters, we found that the mean systolic blood pressure before spinal anaesthesia and the lowest mean systolic blood pressure and lowest mean diastolic blood pressure did not differ significantly between the three groups. None of the patients developed symptomatic bradycardia (<50 bpm) or hypotension defined as a decrease in mean arterial blood pressure by $\geq 20\%$. Lauretti et al⁹ showed similar observations but our study was in contrast to Hood et al⁸ who showed that spinally administered cholinergic agonist or cholinesterase inhibitors increase blood pressure and heart rate. The small dose (50-150 µg of neostigmine) could explain the lack of cardiovascular stimulation seen in our study. Hood et al used 500-750µg of neostigmine in their study.

Table 5: Comparison of Haemodynamic Parameters in three groups

Blood Pressure (mmHg)	GROUP A	GROUP B	GROUP C
Highest Systolic (Pre- operative)			
Mean Systolic	125.13±5.84	126.20±5.16	125.80±4.88
Absolute(highest) Systolic	130	130	138
Highest Diastolic (Pre- operative)			
Mean Diastolic	79.20±5.60	78.07±5.67	77.73±5.96
Absolute(highest) Diastolic	79	78	92
Lowest Systolic (Intra operative)			
Mean Systolic	118.0±8.05	119.73±5.94	119.73±5.30
Absolute(lowest) Systolic	104	106	108
Lowest Diastolic (Intra operative)			
Mean Diastolic	79.27±6.11	78.47±6.34	78.07±6.69
Absolute(lowest) Diastolic	60	64	62

Mean oxygen saturation (SpO₂) and respiratory rate were comparable between the three groups and other similar studies^{8,10} with no patient developing hypoxemia (SpO₂ < 90%). There is no reported evidence of respiratory depression with the use of intrathecal neostigmine.

The highest sensory level achieved and time for onset of sensory block and onset of motor block (Bromage Grade II) were compared and were observed not to reach a statistically significant difference. The time for two segment regression of sensory block was prolonged in both the 50µg group (127.6 ± 6.03) and 150 µg group (140.67 ± 4.54) as compared to the control group (115.23 ± 2.73) and showed a statistically significant difference of <0.001. Liu et al¹⁰ and Pan et al¹¹ demonstrated similar prolonged durations of sensory block in their studies.

Duration of motor block is significantly prolonged in the neostigmine 150µg group (220.30±9.30) and the neostigmine 50µg group (197.0±7.01) as compared to the Bupivacaine control group (189.83±5.64), the comparison being statistically significant as was shown by similar dose neostigmine studies of Liu et al¹⁰ Tan et al¹² and Pan et al¹¹. Intrathecal neostigmine causes motor block by acetylcholine mediated reduction in motor neuron outflow with no reduction in spinal cord blood flow or histopathological changes⁸. In addition increased spinal levels may augment motor block of spinal bupivacaine^{10,12}.

Analgesia provided by intrathecal neostigmine as assessed by visual analogue scale was also observed. VAS scores were compared at 1,2,3,4,6,8,10,12 and 24 hour durations and showed a statistically significant (p<0.05) value when the 50 and 150 µg neostigmine groups were compared with the control group. Our results are in agreement with Chung et al¹³ and Lauretti et al¹⁴ who demonstrated statistically significant lower visual analogue scale scores in the doses ranging from 25-75µg neostigmine group compared to saline group and studies done by Klamt et al¹⁵ and Hood et al⁸.

The analgesic effects of cholinergic agonists and anticholinesterase agents have been demonstrated in several species including humans. Intrathecal administration of neostigmine produces analgesia in healthy volunteers by a spinal action in a dose dependent manner and the effective dose does not cause any neurological or cardio respiratory changes.^{8,16} Auto radiography have demonstrated muscarinic binding in the substantia gelatinosa and to a lesser extent in laminae III and V of gray matter of the spinal cord.² The effects of spinal neostigmine and edrophonium emphasize the relevance of the release of endogenous acetylcholine from spinal systems.¹⁷ This reflects that anti nociception is produced by inhibition of transmitter (ACh) metabolism. Although spinally administered agonist produce analgesia in all species tested, analgesia from cholinesterase inhibition depends on the degree of spinal cholinergic tone.⁸

The total duration of analgesia was 263.30±7.57 Hrs, 340.10±8.36 hrs and 700±8.65 hrs in control group, 50µg neostigmine and 150µg neostigmine respectively and showed

statistically significant difference (p<0.05) when compared between the three groups.

All the patients were observed for any possible complications. Vomiting showed a statistically significant difference (p <0.05) between the control and study groups. Other similar studies done by Hood et al⁸, Lauretti et al⁹, Klamt JG¹⁵ etc. showed similar increase in the incidence of nausea and vomiting with similar dosages of neostigmine.

Conclusion

Intrathecal neostigmine results in effective analgesia postoperatively. Further it prolongs sensory and motor block induced by bupivacaine spinal anaesthesia and at the same time cause no haemodynamic or ventilator depression in the intraoperative and postoperative period. An increase in the incidence of nausea and vomiting was observed in both groups of neostigmine use.

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