Original Article

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Prospective Randomized Double Blind Study to Evaluate the Analgesic Efficacy of Low Dose of Intrathecal Neostigmine in Combination with Fentanyl and Bupivacaine for Lower Abdominal and Lower Limb Surgery

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Abstract

Background: More than 80% of patients undergoing surgical procedures under spinal anesthesia experience acute post-operative pain. The present study was conducted with aim to compare the analgesic efficacy and side effects of addition of neostigmine to fentanyl and bupivacaine. **Subjects and Methodology**: The study was conducted at Christian Medical College and Hospital, Ludhiana in the Department of Anaesthesia and Critical Care, from 15^{th} Oct 2015 to 14^{th} Oct 2016. 50 patients aged between 18 - 60 years belonging to the ASA grade I & II undergoing elective surgery for lower abdominal and limb region (likely to finish within 3 hours), were divided into 2 groups(25 each) . Group A was given Intrathecal Bupivacaine 12.5 mg (2.5 ml) + Fentanyl 20 μg (0.4 ml)+0.1 ml Normal Saline (Total 3 ml) and Group B was given Intrathecal Bupivacaine 12.5 mg (2.5 ml) + Fentanyl 20 μg (0.4 ml) + Neostigmine 1μg (0.1 ml) (Total 3 ml). Various parameters such as sensory and motor block onset, point of maximum sensory level attainment, VAS pain score, rescue analgesia and adverse effects were recorded. **Results:** The results showed that both the groups showed statistically significant difference in terms of sensory blockade and recovery of sensory blockade was. It was observed that group B showed the early onset of sensory blockade and prlonged recovery time. No difference was seen in maximal sensory blockade. **Conclusion:** Intrathecal neostigmine precipitated the onset of motor and sensory blockade and prolongs the block significantly when used with bupivacaine and fentanyl in spinal anesthesia in a low dose. The duration of analgesia was also significantly prolonged when neostigmine is added. Although the addition of neostigmine produced side effects like nausea and hypo tension, they were not statistically significant and were cautiously managed.

Keywords: Spinal Anesthesia, Intrathecal, Fentanyl, Neostigmine

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Introduction

Intrathecal (IT) neostigmine can be used in conjunction with spinal anaesthesia (SA) to reduce acute perioperative pain.[1] It increases the effect of opioid analgesia while minimising unwanted side effects.[2] Although this multimodal pain therapy approach ie combining spinal neostigmine and spinal opioids is effective it could lead to significant systemic side effects such as nausea and vomiting, at doses higher than 6.25 mcg.[2] Thus in the present study we have evaluated the analgesic effect and safety of low dose of intrathecal neostigmine in combination with bupivacaine and fentanyl for spinal anaesthesia.[3–5]

Subjects and Methods

Study Design: Prospective, randomized, double blind study.

Study Population: Approval from institutional ethical committee was taken. The research was conducted at Christian Medical College and Hospital, Ludhiana in the Department of Anaesthesia and Critical Care, from 15^{th} Oct 2015 to 14^{th} Oct 2016. 50 patients aged between 18 to 60 years of either sex belonging to the ASA grade I & II undergoing elective surgery for lower abdominal and limb region (likely to fin-

ish within 3 hours), were divided into 2 groups (25 each). Patients with history of allergy to neostigmine/fentanyl/ bupivacaine, intracranial pressure/convulsions, patient with bleeding diathesis, pregnant women, any dysarrythmias on ECG, any contraindication for spinal anaesthesia which includes infection at the injection's site, existing neurologic condition and surgery lasting for more than 3 hours were excluded from the study. Also informed consent was taken from all patients included in the study.

Under strict aseptic conditions, a 25 gauge Quincke spinal needle was used to administer a subarachnoid block at the L2-3 or L3-4 vertebral stage. Following the block, the patients were made supine. The intra-operative data was recorded by the anaesthesiologist who performed the block. GROUP A received Intrathecal Bupivacaine 12.5 mg (2.5 ml) + Fentanyl 20 μg (0.4 ml)+0.1 ml Normal Saline (Total 3 ml) GROUP B received Intrathecal Bupivacaine 12.5 mg (2.5 ml) + Fentanyl 20 μg (0.4 ml) + Neostigmine 1μg (0.1 ml) (Total 3 ml)

Age, gender, weight, height, BMI, duration of surgery, pre-op heart rate(HR), systolic Blood pressure(SBP), diastolic Blood pressure(DBP), and oxygen saturation(SPO2) of every patient was recorded. PR, BP, and SPO2 were measured at different time interval. A pin-prick test in the mid-axillary line was used to determine sensory blockade. Modified Bromage Score was used to determine motor block. Sensory and motor blockade were measured every two minutes for the first 10 min of the procedure and then every 2 minutes after that. The highest level of sensory block and its onset time time it took for sensory and motor block to recover was calculated as two dermatomes of anaesthesia regression from the maximum level. The VAS-Rating approach was used to measure patient's pain levels. Subjects were also monitored for various side effects after spinal injection which includes nausea, vomiting, hypotension, desaturation, bradycardia, and others.

Statistical Analysis

The data collected was entered using Microsoft Excel Spreadsheet. Data was subjected to statistical analysis using SPSS Version 21. Paired t-test, Student t-test, and chi square test were used. The level of significance at P<0.05 was considered statistically significant.

Results

[Table 1] shows the mean time for sensory block onset in group A was 7.3 ± 0.98 min, while the mean time for sensory block onset in group B was 3.28± 0.66 min. Significant difference was observed when both the groups were compared statistically with group B showing the onset of sensory block slightly earlier(p value<.0001) table 2 shows In group A out of 25 patients, 12 patients (48%) attained maximum sensory level up to T8, 13 patients (52%) attained maximum sensory level up to T10. In group B out of 25 patients, 32% patients (8) attained maximum sensory level up to T10, 60% patients (15) attained maximum sensory level up to T8, and 8% patients (2) attained level till T6. Both the groups were comparable regarding maximum sensory level when subjected to statistical analysis, (p value>.05). On comparing both the groups in terms of recovery time significant difference was seen with recovery time of sensory block was significantly earlier in group A. (p value<.0001). [Figure 1] Table 3 predicts that in group A, the mean time of onset of motor block was 12.48±1.87 whereas in group B, the it was 6.74 ±1.63 minute with statistically significant difference between both the groups (p value<.0001). [Figure 2] depicts that On comparing both the groups the significant difference between both the groups was observed with recovery time of motor block earlier in group A. (p value<.0001). The VAS score was lower in group B because the duration of Sensory and motor block was increased in Group B. [Figure 3& 4] The time for first request of rescue analgesia was significantly earlier in group A. (p value<.0001). fig 5 showed There was no statistical significance in adverse effect between two groups (p value>.05).

Table 3: Onset time of motor block(in minutes)

Onset time of motor block(in minutes)	Group A(n=25)	Group B(n=25)	P value
Mean ± Stdev	12.48 ± 1.87	6.74 ± 1.63	<.0001
Median	13	7	
Min-Max	9-15	4-10	

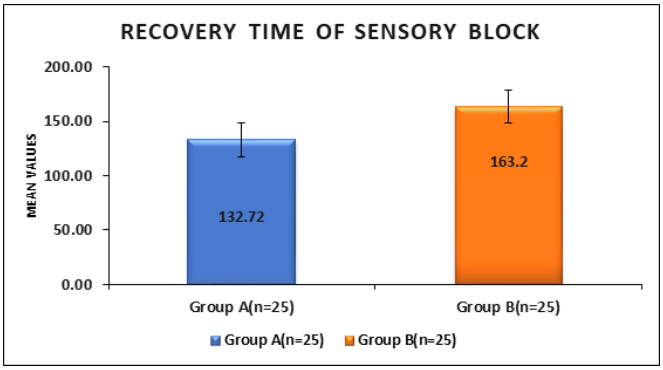

Figure 1: Recovery time of sensory block

Discussion

The mean age of patients in our study was 32.98 ± 12.86 years. The age and gender distribution, demographic characteristics

Table 1: Onset time of sensory block (in minutes)

Onset time of sensory block(in minutes)	Group A (n=25)	Group B (n=25)	P value
Mean ± Stdev	7.3 ± 0.98	3.28 ± 0.66	<.0001
Median	7	3	
Min-Max	6-9	2-5	

Table 2: Maximum sensory level

Maximum level of sensory block	Group A(n=25)	Group B(n=25)	Total	P value
T6	0 (0.00%)	2 (8.00%)	2 (4.00%)	0.172
T8	12 (48.00%)	15 (60.00%)	27 (54.00%)	
T10	13 (52.00%)	8 (32.00%)	21 (42.00%)	
TOTAL	25 (100.00%)	25 (100.00%)	50 (100.00%)	

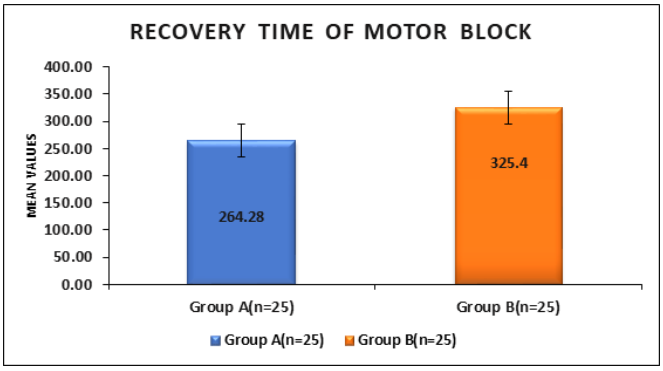

Figure 2: Recovery time of motor block. (GROUP A: Intrathecal Bupivacaine 12.5 mg (2.5 ml) + Fentanyl 20 μg (0.4 ml)+0.1 ml Normal Saline GROUP B: Intrathecal Bupivacaine 12.5 mg (2.5 ml) + Fentanyl 20μg (0.4 ml) + Neostigmine 1μg (0.1 ml)

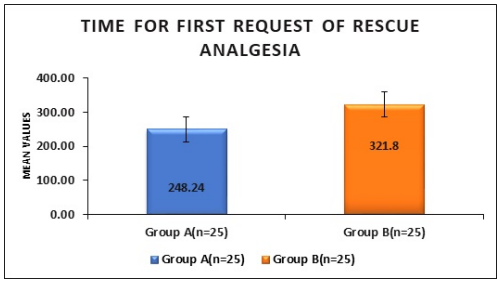

Figure 4: Time for first request of rescue analgesia. (GroupA: Intrathecal Bupivacaine 12.5 mg (2.5 ml) + Fentanyl 20 μg (0.4 ml)+0.1 ml Normal Saline Group B: Intrathecal Bupivacaine 12.5 mg (2.5 ml) + Fentanyl 20μg (0.4 ml) + Neostigmine 1μg (0.1 ml)

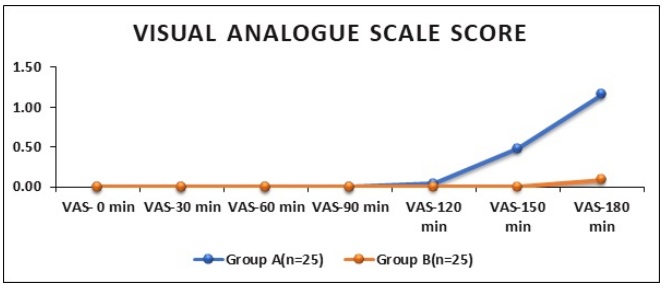

Figure 3: Visualanalogue scale score. (GroupA: Intrathecal Bupivacaine 12.5 mg (2.5 ml) + Fentanyl 20 μg (0.4 ml)+0.1 mlNormal Saline GROUP B: Intrathecal Bupivacaine 12.5 mg (2.5 ml) + Fentanyl 20μg (0.4 ml) + Neostigmine 1μg (0.1 ml)

like Height, weight and BMI were also comparable in both the groups. The pre-op baseline clinical characteristics studied were SBP and DBP (mm Hg), HR (per minute), SPO_2, and all were comparable in both the groups. Hemodynamic stability was comparable in both the groups till the end of follow up postoperatively.

For post-operative pain relief, Shakya ML et al,[3] compared IT fentanyl and IT neostigmine and showed no significant difference in the mean of heart rate between the groups as seen in present study. Tekin et al,[4] his study, found no significant difference in the mean arterial pressures and oxygen saruration at baseline and at 24 hours between all the groups as seen in our study. Similar results were shown by Shakya ML et al,[3] and Jain A et al,[1] also the intraoperative hemodynamic

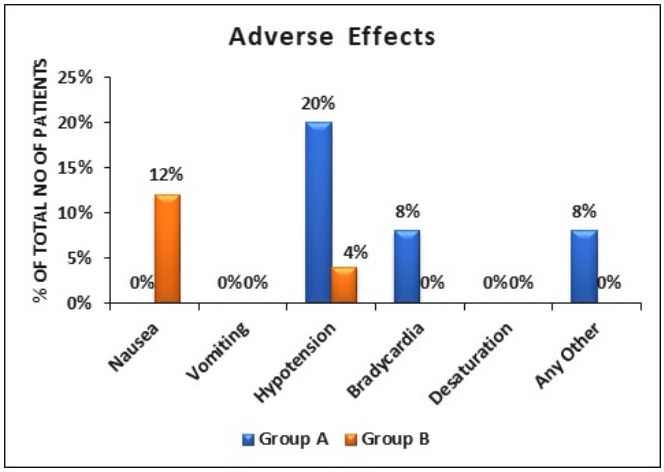

Figure 5: GroupA: Intrathecal Bupivacaine 12.5 mg (2.5 ml) + Fentanyl 20 μg (0.4 ml)+0.1 mlNormal Saline Group B: Intrathecal Bupivacaine 12.5 mg (2.5 ml) + Fentanyl 20μg (0.4 ml) + Neostigmine 1μg (0.1 ml)

characteristics were comparable.

The mean time for sensory block onset in group B was earlier (p value<.0001) thus signifying that in the early stages of sensory blockade, neostigmine was helpful.

Shakya ML et al,[1] in their study results showed No significant difference in the mean onset of sensory block using Neostigmine + bupivacaine (246.57±95.56 s) and fentanyl + bupivacaine (263.97±50.92 s) which in discordance with our study. Whereas in a study by Raghavan R K et al,[5] was the onset of sensory block was 3.97 min with 25 mcg of neostigmine and 3.87 min with 50 mcg of neostigmine which was comparable with our study. Neostigmine induces analgesia by inhibiting the degradation of acetyl choline. The release of nitric oxide in the spinal cord also prolongs and intensifies the analgesic effect.

Both the groups were comparable regarding maximum sensory level when subjected to statistical analysis, (p value>.05). [Table 2]. No additional effect of neostigmine was seen on maximum sensory level achieved in our study. Jain A et al,[1] in his study also found no statistical significance between two groups (p value>.05). Maximal sensory block level in both the groups was T7. On comparing both the groups in terms of recovery time it was inferred that addition of Neostigmine prolonged the duration of Sensory block similar results were shown by Jain A et al and Tekin et al in their study.[1,4]

In present study the mean time of onset of motor block showed statistically significant difference between both the groups (p value<.0001) which inferred that Neostigmine helped in the early onset of motor blockade. In a study by Fareed A et al,[6] the time for the onset of motor block was 8.44±1.05 minutes, and 8.46±0.71 minutes. There was no statistically significant difference among the study groups (p>0.05). Our study result did not corroborate with them or other studies by Harbhej Singh et al,[7] Diana F Gabinsky et. Al,[8] and U Srivastava and coworkers.[9] In a study by Sharma R et al,[10] the onset of motor block was 12.4 mins and it was also significantly less than the control as seen in our study.

IT Neostigmine induces motor block by reducing motor neuron outflow through Acetyl choline, with no changes in spinal cord blood flow or histopathology. Furthermore, increased acetylcholine levels in the spinal fluid can enhance the motor blockade caused by spinal bupivacaine.[5]

Our study showed that that addition of Neostigmine prolonged the duration of Motor block. Jain A et al,[1] in his study also found statistical significance between two groups (p value<.05). Our study findings did not match the study by Fareed A etal,[6] in which the duration of motor block was 121±13.52 minutes, and 126±6.1minutes. There was no statistically significant difference among the groups (p>0.05). Similar non significant results were seen by Harbhej Singh et al and Diana F Gabinsky et. al.[7,8]

The time for first request of rescue analgesia was significantly earlier in group A. (p value<.0001). Bhavsar M et al, showed that mean time to rescue analgesia in the Neostigmine, fentanyl and bupivacaine group was 476.7 min. According to animal study by Wang et al the potential synergism was observed between fentanyl and neostigmine along with bupivacaine.[10,11]

The efficacy and safety of intrathecal neostigmine at doses of 50 and 150 mg as an adjuvant to bupivacaine for postoperative analgesia under spinal anaesthesia were investigated by Pandey V et al.[12] The average time of analgesia in Group I with bupivacaine was 224.40 ±23.28 minutes, 367.60 ±42.15 minutes in Group II with 50 mcg Neostigmine, and 625.60± 87.70 minutes in Group III with 150 mcg Neostigmine. As seen in our research, the need for rescue analgesia in the form of injection diclofenac sodium 75 mg intramuscularly was significantly lower in both study groups (P 0.05).

Lauretti et al. found that the time of rescue analgesia for IT fentanyl and neostigmine was shorter than when both drugs were used together.[13]The addition of a low dose of neostigmine increased the length of complete analgesia and effective analgesia by 75% and 78 percent, respectively, according to Jain A et al.[1] Akinwale MO et al,[14] same results in their study conducted to determine efficacy of the analgesic and adverse effects of intrathecal neostigmine in combination with hyperbaric bupivacaine and fentanyl. Overall VAS scores were found to decrease with Neostigmine in other studies of Jain A et al,[1] and Tekin et al.[4] Bhavsar M et al,[11] in their study obtained similar results as present study.

It was mostly due to the combined use of both medications, which synergized their effects and resulted in a longer period of rescue analgesia.

There was no statistical significance in adverse effect between two groups (p value>.05). Hypotension was caused by sympathetic nervous system blockade during subarachnoid block, which resulted in lower systemic vascular resistance and cardiac output. The addition of neostigmine to bupivacaine intrathecally did not reduce hypotension. In contrast, some studies had observed that intrathecal neostigmine can counteract the hypotension induced by intrathecal local anesthetics by directly stimulating preganglionic sympathetic neurons in spinal cord.[12]

Jain A and coworkers in their research showed similar results as was seen in our study.[1]

Lauretti et al found that higher dose of Neostigmine was associated with more side effects than low dose Neostigmine.[13] In a study by Akinwale MO,[14] the incidence of adverse effects such as hypotension, bradycardia, nausea and vomiting were not statistically significant in both groups ($p > 0.05$).

In a study, Pandey V et al found that the frequency of nausea and vomiting was higher in the 150 g neostigmine group than in the 50 g neostigmine group

Neostigmine is responsible for inhibition of spinal cholinesterase leading to the production of more endogenous acetylcholine, which is possibly released by intrinsic cholinergic neurons in the dorsal horn of the spinal cord. These cholinergic neurons terminate in the vicinity of primary afferent express muscarinic receptors. The endogenous acetylcholine produces analgesic effect through muscarinic presynaptic inhibition of glutamatergic afferents, similar to how it has been described in the neostriatum. Muscarinic receptor antagonists have been shown to reverse the analgesic effects of IT neostigmine. A tonic cholinergic activity is an important prerequisite for the effectiveness of neostigmine.[15–18]

The increased analgesic efficacy of IT neostigmine is due to increased spinal acetylcholine release from more severe and sustained postoperative pain, and subsequent action at muscarinic M1 and M3 and presynaptic nicotinic receptors found in cholinergic interneurons in the dorsal horn's lamina III and V. It's also been proposed that nicotinic receptors in the dorsal horn ganglion and the spinal meninges are involved.

In conclusion, low dose IT Neostigmine can be considered as a safe drug to increase the efficacy of anaesthesia intra operatively and post operatively when added to IT bupivacaine and IT Fentanyl thereby reducing the need of additional analgesics.[19]

Conclusion

- Intrathecal neostigmine precipitated the onset of sensory and motor blockade and prolonged the sensory and motor block significantly when used with fentanyl and bupivacaine in spinal anesthesia in a low dose.
- There was no significant hemodynamic instability in our patients. The maximal upper level of sensory block achieved was not higher on addition of intrathecal neostigmine.
- The duration of analgesia was significantly prolonged among the neostigmine added groups as indicated by the time of first rescue analgesia.
- Although the addition of neostigmine produced side effects like nausea and hypo tension, they were not statistically significant and were cautiously managed.

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