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Original Research Article

A comparative evaluation of the analgesic efficacy of low doses of intrathecal neostigmine and bupivacaine with plain bupivacaine in lower limb surgery

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ABSTRACT

Background and Aims: Intrathecal neostigmine prolongs the duration of analgesia and also appropriate dose reduces the associated side effects. The present study was conducted to evaluate the analgesic efficacy, identify the optimum dose using 3 different doses of neostigmine in combination with bupivacaine in comparison with bupivacaine alone for the intra & postoperative period.

Materials and Methods: Eighty patients of ASA I & II undergoing lower limb surgery under spinal anaesthesia were enrolled and divided into 4 groups of 20 each. Group I: bupivacaine control group, Group II: Bupivacaine + 12.5 μgm Neostigmine, Group III: Bupivacaine +25 μgm Neostigmine, Group IV: Bupivacaine + 50μgm Neostigmine. Hemodynamic parameters, sensory and motor characteristics and adverse effects if any were noted. Pain was assessed using visual analog scale (VAS) in postoperative period hourly for 12 hours & then at 24hours. Onset, duration and level of sensory block were recorded along with onset and duration of motor block.

Results: Largest dose (50mgm) produced an increase in duration of analgesia by 16.60min (an increase of 20.10%) compared to control group. The 25mgm intrathecal neostigmine resulted in an increase of 7.20min (an increase by 8.25%).

Conclusion: The dose of 50mgm neostigmine in comparison with 25mgm dose significantly prolonged the duration of two segment regression, effective and complete analgesia, with no increase in the incidence of nausea and vomiting and hence 50mgm appears to be the optimum dose amongst the doses considered in our study for intrathecal administration in lower limb surgery.

1. Introduction

Pain has been a major concern of human kind since our beginnings, and it has been the object of ubiquitous efforts to understand and to control it. We as anaesthesiologists have played a pivotal role in adequately managing pain for the patients and also providing optimal and comfortable working conditions for our fellow surgeons. Nowadays, many surgeries (because of their localized peripheral sites) are carried out under regional anaesthesia techniques as it offers several advantages over general anaesthesia namely, decreased incidence of respiratory and cardiac depression, improved perfusion via sympathetic blockade, reduced blood loss and decreased risk of thromboembolism and improved and early post-operative analgesia.In a developing country like ours, cost of anaesthesia is also an important determinant, being substantially lower in regional technique.

In regional anesthesia, intrathecal local anesthetics have been commonly used for providing analgesia in doses ensuring patient safety. Attempts have been made to prolong analgesia duration by addition of various adjuncts to local anaesthetic agents viz. vasoconstrictors, opioids, α2 adrenergic agonists. However no ideal intrathecal adjunct

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has been found so far.

Neostigmine, an anticholinesterase agent, enhances the sensory blockade in a novel manner. It inhibits breakdown of endogenous spinal neurotransmitter acetylcholine[1] that is involved in modulation of nociception through muscarinic receptors in lamina I-III of dorsal horn of spinal cord.

Studies have shown that intrathecal neostigmine lessens bupivacaine induced hypotension, potentiates analgesic efficacy of intrathecal morphine & clonidine, has no cardiorespiratory depressant effects nor any decrease in spinal cord blood flow, an important indicator of neurotoxicity.[1] It is also not associated with side effects like sedation, pruritus in doses used clinically. But, neostigmine in doses used clinically, produced severe nausea & vomiting and prolonged motor block, which was dose dependant which can markedly decrease patient acceptance. Neostigmine at lower dosages improve the quality of anaesthesia, prolong post-operative analgesia with fewer side effects. Hence, in our study we intented improvement in the quality of analgesia both intra operatively and post operatively using low doses of intrathecal neostigmine in combination with bupivacaine in patients undergoing lower limb surgeries, and to identify its optimum dose.

2. Materials and Methods

Our study was a prospective randomized study conducted in the Department of anesthesiology and critical care at a tertiary hospital in New Delhi after taking institutional ethical committee approval. A written informed consent was taken from patients selected for the study.

A total of 80 adult patients of either sex, American society of anesthesiologists (ASA) physical status I-II in the age group of 20-80 years scheduled for elective surgery involving internal fixation of femur under spinal anaesthesia were taken up for the study. Patients having any contraindication to regional technique viz. local infection, coagulation disturbance, sepsis, spinal deformities, previous spinal surgeries, neurological diseases, patient refusal or those being allergic to test drugs were excluded from the study.

Eighty patients were randomly divided into four groups (20 patients in each group) using random number table. In Group I (control group) patients received, 2.5ml of 0.5% Heavy Bupivacaine + 0.5ml Normal Saline. Group II patients, received 2.5ml of 0.5% Heavy Bupivacaine + 0.5ml Normal Saline containing 12.5 μgm Neostigmine. Group III patients received 2.5ml of 0.5% Heavy Bupivacaine +0.5 ml Normal Saline containing 25 μgm Neostigmine. Group IV patients received 2.5ml of 0.5% Heavy Bupivacaine +0.5ml Normal Saline containing 50μgm Neostigmine.

A day prior to surgery, preanaesthetic evaluation was done and routine investigations were sent. The concept of visual analog scale (VAS) which consisted of a 10 point scale with 0 as no pain and 10 as worst imaginable pain & VAS nausea score which consisted of a 10 point scale with a 0 as no nausea and 10 as worst imaginable nausea was explained to the patient.

All the patients were kept fasting from midnight till surgery and were premedicated with Tablet Diazepam 0.2 mg/kg on the night before surgery. In th operation theatre, the monitors are placed and the patients were preloaded with lactated Ringers Solution 15 ml/kg over 15-20min. Under all aseptic precautions, lumbar puncture was performed by the midline approach in the sitting position using 25G Quincke needle in the L3-L4 interspace. After obtaining free flow of C.S.F., drug solution of the concerned group was injected at the rate of 0.2ml/second with the bevel of the needle pointing cephalad. The drug to be administered was prepared freshly by a second anaesthesiologist otherwise uninvolved in the study. The anaesthesiologist performing the block and assessment was blinded to the nature of drug administered. Time to intrathecal injection was noted and the patient turned supine immediately and kept supine for 15 minutes before positioning for surgery. During the entire surgery oxygen supplementation was provided via a ventimask. Patients with inadequate anaesthesia were excluded from the study. No analgesics or sedatives were given intraoperatively.

Pulse rate, oxygen saturation (SpO_2), respiratory rate and noninvasive blood pressure-systolic and diastolic blood pressure were continuously monitored every 5 minutes intraoperatively and every hour for 12 hours postoperatively. Bradycardia defined as <50 beats per minute was treated with incremental injections of atropine 0.3 mg iv. Hypotension defined as fall in systolic blood pressure to less than 90mm Hg. or fall of more than 20% from baseline values was treated with additional fluids and incremental doses of Inj. Mephentermine 3 mg. Respiratory depression was defined as respiratory rate less than 10 breath per minute. The onset of sensory block i.e time from intrathecal injection till highest sensory block was achieved tested by loss of pin prick needle. The level of sensory block was tested by loss of pin prick sensation in the midclavicular line, bilaterally every 2 minutes till maximal level was achieved and then every 15 minutes till two segment regression, using a 25G hypodermic needle. Duration of analgesia was noted as the time from intrathecal injection till two segment regression. Post operatively VAS Score (pain) was recorded hourly till 12 hours and then at 24 hours. Time was noted when VAS pain score was greater than 4 or when the patient requested for 1^{st} rescue analgesic. Duration of Complete Analgesia was noted as time from intrathecal injection to 1^{st} complaint of pain. Duration of effective analgesia was noted as time from intrathecal injection to 1^{st} rescue analgesia. Number of analgesics in 24 hours was noted. Injection Diclofenac 1.5 mg/kg i.m. upto maximum 75mg was administered and not

repeated before 6 hours.

The onset of Motor Block i.e time from intrathecal injection to maximal motor block-modified Bromage Scale: Grade 3 was recorded. (Modified Bromage Scale: 0 = full movement; 1 = inability to raise an extended leg can bend the knee; 2 = inability to bend the knee, able to flex the ankle; 3 = no movement.) Duration of Motor Block was assessed half hourly till Grade I modified Bromage Scale was achieved. Nausea was assessed on 10 cm VAS Score with 0 equaling no nausea and 10 worst possible nausea at 15 min. after intrathecal injection and then half hourly till the end of surgery. Postoperatively, nausea was recorded hourly for 12 hours and then at 24 hours. The frequency and severity (mild, moderate and severe) of vomiting was noted intra and postoperatively. VAS>2 nausea or vomiting was treated with iv injection ondansetron 4 mg.iv. Any other side effects viz. bradycardia, sweating, anxiety, sedation was noted.

The data was analysed by using SPSS version 22. The statistical technique used in analysis were one way Analysis of Variance (ANOVA), Chi-square test and fisher exact test. The multiple range test was applied to see the significant pairs contributing towards the overall significance in ANOVA. The significance was taken if p value<0.05. All the data are expressed as mean + SD wherever applicable.

3. Results

In our study all the four groups were comparable with regards to demographic characteristics such as age, sex distribution, height, weight and duration of surgery. The mean age of patients in Group I was 46.05 ± 15.3 years, in Group II 45.75 ± 17.65 years, and in Group III 42.55 ± 17.08 years and in Group IV was 41.20 ± 15.63 years. The mean weight of patients in Group I was 74.24 ± 8.23 kg, in Group II 73.50 ± 10.21 kg, in Group III 77.36 ± 12.20 kg and in Group IV 80.55 ±12.34kg.The mean height of patients in Group I was 168.75 ± 5.34 cm, in Group II 168.14 ± 6.31 cm, in Group III 168.18 ± 7.24 cm and in Group IV 168.25 ± 8.44cm. The sex distribution among the groups showed 14 males and 6 females in Group I, 13 males and 7 females in Group II and IV, and 15 males and 5 females in Group III and the difference was not statistically significant. The four groups were also comparable in terms of duration of surgery. The mean duration of surgery in Group I was 120.30 ± 22.4min, in Group II was 126.30± 25.3min, and in Group III was 125.30 ± 25.9min and in Group IV was 127.30 ± 22.87min.

All the four groups were statistically comparable for the time to onset and the level (dermatome) of maximum sensory block as shown in Table 1. Statistically significant difference was found in the mean duration of analgesia i.e. two segment regression between the four groups. (Table 1) On further intergroup comparison, statistically significant increase in duration of analgesia was observed between the groups. Group III (25μgm neostigmine) & Group IV (50μgm neostigmine) significantly prolonged the regression time compared to control group (Group-I) by 7.20 min & 16.60 min respectively (p value < 0.05). Statistically significant difference in the mean duration of complete analgesia was observed between the four groups. On intergroup comparison, statistically significant increase in the mean duration of complete analgesia was observed between Group III & Group I (an increase by 15.87%) and Group IV & other 3 groups. Group IV showed the maximum mean duration of complete analgesia as 274.20 min as compared to the other groups as shown in table 1.

Onset of motor block was statistically comparable between the four groups. Statistically significant difference in the mean duration of motor block was observed between the four groups. (Table 2). On intergroup comparison, statistically significant increase in mean duration of motor block was observed between Group IV and Group I (increase of 37.20 min), Group IV and Group II (increase of 31.50 min), Group IV and Group III (increase of 27.90 min).

Group IV showed statistically significant prolongation in duration of motor block compared to control group (Group I).

Hemodynamic parameters such as pulse rate, noninvasive blood pressure and respiratory rate remained statistically comparable between the four groups intra and post operatively.Statistically significant decrease in mean postoperative analgesic requirements was observed in first 24 hours (Table 3) between Group III & Group I (decrease of 16.66%), Group IV & Group I (decrease 23.07%), Group III & Group II (decrease of 13%) and Group IV & Group II (decrease of 20%).

VAS pain scores at the time of first rescue analgesic showed no significance statistically on comparing the four groups as shown in Table 4.(p value=0.995)

Statistically significant difference in the total number of patients complaining of nausea and vomiting was observed between the four groups. (Table 5) Statistically significant difference was observed between Group IV & Group I and Group IV & Group II. There appeared a borderline significant difference (p value=0.05) in the number of patients requiring rescue emetics. No such differences was found on applying fisher exact test.

4. Discussion

Intrathecal acetylcholinesterase inhibitors have been shown to produce antinociception in animals,[2–4] volunteers,[5,6] in acute[7,8] and chronic[9] pain states. The degree of antinociception depends upon the spinal cholinergic tone. The antinociceptive effect is mediated via spinal muscarinic, nicotinic[10,11] receptors and indirectly through the release of second messenger NO, which are involved in the modulation of sensory afferent input reaching the spinal

Table 1: Sensory block characteristics

	Group-I	Group-II	Group-III	Group-IV	P value
Onset of Sensory block (min) Mean±SD	8.00±1.36	8.35± 1.18	8.65± 1.26	8.90± 1.88	0.652
Level of maximum Sensory Block (dermatome) Mean	T7	T7	T8	T8	0.164
Duration of Analgesia (min) Mean±SD i.e 2 segment regression	85.55±8.75	86.75±9.63	89.75±9.96	99.15±7.9	0.000
Duration of Complete Analgesia (min) Mean±SD	195.55± 28.94	210.85±22.54	226.60±27.97	274.20±48.31	0.000

Table 2: Motor block characteristics

	Group-I	Group-II	Group-III	Group-IV	P value
Onset of motor block (min) Mean ± SD	6.85±1.81	5.95±1.28	6.25±1.29	5.85±1.87	0.195
Duration of Motor Block (min) Mean ± SD	157.55 ±14.83	163.25 ±22.22	166.85 ±20.40	194.75± 19.86	0.00

Table 3: Analgesic dose requirement in first 24 hours

Number of Analgesic doses	Group-I	Group-II	Group-III	Group-IV	p value
Mean ± SD	3.90±0.36	3.75±0.44	3.25±0.44	3.00±0.64	0.000

Table 4: Visual analog scale (VAS) pain score at 1st rescue analgesic

	Group-I	Group-II	Group-III	Group-IV	p value
VAS score Mean ± SD	4.95±0.76	4.95±0.60	4.90±0.79	4.95±0.76	0.995

Table 5: Total incidence of nausea & vomiting

	Group-I		Group-II		Group-III		Group-IV		p value
TINV	n	%	n	%	N	%	N	%	0.018
	0	0	0	0	3	15	5	25	

dorsal horn. Thus neostigmine by altering acetylcholine levels in the spinal cord may modulate intrinsic cholinergic pathway which may be pre-and/or post synaptic. Intrathecal neostigmine produced analgesia at much lower doses in acute pain states[7,8] than required for analgesia in volunteers.[5,6] This increase in potency of intrathecal neostigmine results from an increase in release of spinal cord acetylcholine from activation of descending noradrenergic antinociceptive system by ongoing pain[12,13] as compared to volunteers who are exposed to intermittent periods of acute pain.[6]

In our study, intrathecal neostigmine had no clinically significant effect on the cardiorespiratory parameters over the time period observed and dosages used, which is consistent with the observations made in various studies. In contrast Hood D.D et al[5] has shown that spinally administered cholinergic agonist caused increase in blood pressure and heart rate, but they had used larger doses i.e 500-750μgm neostigmine in their study. Lauretti GR et al,[1] Liu SS et al.[6] No episode of arterial desaturation (SpO_2 < 95%) was observed in any patient of the four groups observed, at any point of time.

The mean time to onset of sensory block was 8.00 (1.36) min, 8.35 (1.18)min, 8.65 (1.26)min, 8.90 (1.88) min in Group I, II, III and Group IV respectively. No difference in the time to onset of sensory block was observed in our study similar to those observed by Lauretti GR et al,[8] Saini et al.[14] and Pandey et al.[15] This observation can be explained by the fact that neostigmine being a polar compound, the onset of action can be delayed by 30-40minutes following intrathecal administration.[5,16] On the contrary, Chittora S P et al.[17] had observed a faster onset of sensory block with neostigmine added to lignocaine, this might reflect a different interaction of neostigmine as compared to bupivacaine.

The maximum level (dermatome) of sensory block achieved showed no statistically significant difference in

any of the four groups in our study and this was in corroboration with observations of Klamt J G et al,[18] Lauretti G R et al.[19] The spinal anaesthetic spread is primarily dependent on the dose, baricity, position and height of the patient. Pan P M et al[20] observed an increase in the maximum level of sensory block when neostigmine was combined with bupivacaine and clonidine but observed no such effect when neostigmine was combined with bupivacaine alone.

The mean duration of analgesia (time to 2 segment regression) in our study was 82.55 (8.75)min, 86.75 (9.63)min, 89.75 (8.96)min, 99.15(7.95)min in Group I, II, III and Group IV respectively. In patients who received 25mgm (Group III) and 50mgm (Group IV) statistically significant prolongation in mean duration of analgesia was observed compared to control group. Group IV prolonged the duration of analgesia by 20.10% compared to control group (Group I). The analgesia duration by 50μgm was also statistically significant compared to 12.5 and 25mgm group. This prolongation was due to accentuation of bupivacaine induced nonspecific axonal conduction block by intrathecal neostigmine by increasing C.S.F. levels of acetylcholine.[21] The dose dependency of this mechanism may be explained by observation that neostigmine inhibits acetylcholinesterases at lower concentrations than are required to inhibit butrylcholinesterases. Similar observations have been made by Liu SS et al.,[6] and Yegin A et al.[22] No prolongation in regression times was noted in some studies[3,22] as they either used different concentrations of bupivacaine.

We observed a dose dependent increase in the duration of complete analgesia, predefined as time from intrathecal injection to the first complaint of pain, in our study. The 50mgm group showed an increase in duration by 78.65min (40.2%), 63.35min (30.04%), 47.60min(21.06%) compared to control group, 12.5mgm and 25mgm group respectively. The results of our study are similar to those of Tan PH et al[21] who observed an increase in duration to 373+62.7min compared to 243+16.6min in saline group showing an increase of 52% with 50mgm intrathecal neostigmine. The prolongation of duration of complete analgesia in our study is modest with largest doses (50mgm) prolonging the duration by 78.65min (an increase by 40.21%) compared to control group, whereas Pan PM et al[20] and Klamt J G et al[18] observing 200%, 128% increase in duration probably reflecting differences in the noxious stimuli as patients undergoing vaginal surgeries have over all lower VAS scores and all the patients in these studies were female and neostigmine is shown to be twice as potent in these subjects due to effect of estrogen on spinal cholinergic activity.

In our study, there was no statistical significant difference in the time to onset of motor block with intrathecal neostigmine similar to other studies by Klamt JG et al.,[18] Tan PH,[21] Yegin A et al.[22] that can be explained by hydrophilic nature of neostigmine which leads to time lag of 30-40min in the onset of action. The prolongation of motor block in Group IV (50mgm) was by 23.6%, 19.29%, 16.72% compared to control, Group II and Group III respectively. The duration was prolonged by almost half an hour in Group IV compared to control group. Neostigmine increases the CSF levels of acetylcholine, which in turn inhibits spinal cord motor neuron outflow and may also potentiate bupivacaine induced axonal conduction block. Similar observations have been made by Pan PM et al[20], Yegin A et al[22] and Klamt JG et al.[18] No prolongation was observed in studies by Lauretti GR,[23] Almedia RA et al[24] which used lower doses of neostigmine (1-5mgms).

In our study we observed a dose dependent reduction in the post-operative analgesic requirements in the first post operative day. No significant reduction, in analgesic requirements, was observed in 12.5mgm group compared to control group and between 25mgm and 50mgm group. It seems plausible as hydrophilic nature of neostigmine permits its long residence time in CSF[25] and appreciable levels of neostigmine have been observed in patients even after 24 hrs of intrathecal injection. Synergistic/additive response was observed by Miranda et al.[26] between diclofenac and neostigmine, diclofenac may act by peripheral/supra spinal mechanisms causing inhibition of pain pathways. Some studies show no reduction[7,8,27,28] while others have shown statistically significant reduction[19,20] in post operative analgesic requirements which may reflect differences in the intensity of noxious stimuli, type and mode of administration of post operative analgesia, methods to evaluate the post operative analgesia and the VAS score at which analgesics are given.

Mean VAS score at the first rescue analgesic showed no statistical significance in our study.

Nausea and vomiting is reported to be the major and the most common side effect of neostigmine typically described as dose, baricity, patient position dependant, severe, repetitive, resistant to antiemetic treatment and occurs 60-90 minutes after intrathecal administration, indicating that it is due to cephalad migration of neostigmine in the CSF.[5,21] Our study showed no incidence of nausea or vomiting in control & 12.5mgm group. One patient in 25mgm group and one in 50mgm had an episode of vomiting which responded to Injection Ondansetron. The incidence of nausea was 10% and 20% in 25mgm and 50mgm respectively which also responded to Injection Ondasetron. The combined incidence of nausea and vomiting was 15% and 25% in 25mgm and 50mgm group respectively which was statistically significant in 50mgm group compared to control group. Lauretti GR et al.[27] Klamt JG et al.[18] observed that visceral manipulation is associated with higher incidence of nausea and vomiting than in those undergoing orthopaedic procedures. However, in our study as no operation involved

visceral manipulation and the spinal drug was administered in the sitting position before being turned supine, this minimized the cephalad spread of neostigmine.

5. Conclusion

25mgm and 50mgm neostigmine produced a dose dependant modest increase in time to two segment regression, duration of complete and effective analgesia, duration of motor block and reduced 24 hour post operative analgesic requirements with statistically significant increase in the incidence of nausea and vomiting which was easily treatable. This modest increase in two segment regression and duration of complete analgesia may be of help in prolonged surgeries and in providing early effective post operative analgesia.

The dose of 50mgm neostigmine in comparison with 25mgm dose significantly prolonged the duration of two segment regression, effective and complete analgesia, with no increase in the incidence of nausea and vomiting and hence 50mgm appears to be the optimum dose amongst the doses considered for intrathecal administration in lower limb surgery.

6. Source of Funding

None.

7. Conflict of Interest

The author(s) declare(s) that there is no conflict of interest.

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