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Original Article

COMPARISON BETWEEN INTRATHECAL NEOSTIGMINE AND FENTANYL AS ADJUVANT TO HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA FOR POST-OPERATIVE PAIN RELIEF

MADHUCHANDA BORAH[1], MUKESH PATIR[2*], ESMA ANTONY[3]

[1,2]Department of Anaesthesiology, Assam Medical College and Hospital, Dibrugarh, Assam. [3]Department of Anaesthesiology, Sunrise Hospital, Kochi, Kerala

*Corresponding author: Mukesh Patir; *Email: mukesh_docmp@yahoo.co.in

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ABSTRACT

Objective: Many adjuvants are used during lumbar spinal anaesthesia for lower limb and abdominal surgeries in day-to-day anaesthesia practice. The objectives of the study are to evaluate the time to onset of sensory and motor block, analgesic effect, and side effects of Neostigmine and Fentanyl as an adjuvant to hyperbaric Bupivacaine in spinal anaesthesia.

Methods: 80 patients aged 18 to 60 y of either sex, American Society of Anaesthesiologist (ASA) Physical Status I and II, undergoing elective lower limb and abdominal surgeries under lumbar spinal anaesthesia, were randomly divided into two groups-Group N and Group F, with 40 patients each. Group N received 50 µg Neostigmine and Group F received 30 µg Fentanyl with 03 ml of 0.5% hyperbaric Bupivacaine intrathecally. Intraoperative vitals, onset of sensory and motor block, time to first rescue analgesia, and side effects were recorded.

Results: There was no significant difference in the time to the onset of sensory block, peak sensory block (T_6) and motor block in both groups (p-value>0.05). However, the two-segment block regression was slower, and the time to rescue analgesia was delayed in Group N than in Group F (p-value<0.0001). Except for nausea and vomiting, other side effects like hypotension, bradycardia, etc., were not significant and managed successfully.

Conclusion: Both Neostigmine and Fentanyl are safe and effective adjuvant to hyperbaric Bupivacaine in spinal anaesthesia for post-operative analgesic effect. However, due to the higher incidence of nausea and vomiting, the use of Neostigmine as an adjuvant is limited.

Keywords: Lumbar spinal anaesthesia, Hyperbaric bupivacaine, Neostigmine, Fentanyl, Lower limb and abdominal surgery

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INTRODUCTION

Perioperative pain management is an integral component to patient care and outcome. Lumbar spinal anaesthesia is most common and popular anaesthetic technique for patient undergoing lower limb and lower abdominal surgeries; considering it as a safe and effective technique with profound analgesia, muscle relaxation and lesser general anesthesia-related potential issues. Commonly used amide local anaesthetic, Bupivacaine, has a limited duration of action when used alone. Various research works have been going on for decades in search of an ideal adjuvant alone or in combination to intrathecal local anaesthetic to enhance post-operative analgesia with minimum side effects. So, various non-opioids and opioids have been studied till date [1]. Effective peri-operative analgesia reduces noxious input and thereby attenuates the pathophysiological changes; facilitate to improve morbidity and mortality. The most dominant response to pain involves hypothalamic-pituitary-adrenocortical and sympathoadrenal interaction. Poorly controlled post-operative analgesia result a range of harmful acute and chronic effect [2]. Neostigmine methyl sulphate, a quaternary amine compound, prevents hydrolysis of Acetylcholine (Ach) by Acetylcholinesterase Enzyme (AchE) at the cholinergic transmission site and enhances the response to Acetylcholine that is spontaneously released from the nerve. Acetylcholine itself is an anti-nociceptive [3]. Intrathecal Neostigmine prevents Acetylcholine destruction via muscarinic and cholinergic receptors located at dorsal horn of the spinal cord, substantia gelatinosa and in lesser amount at lamina II and V. The side effects are dose-dependent [4]. Spinal anaesthesia provide a basic component of acute pain management when an adjuvant is added to the local anaesthetic, and thus reduce overall Non-Steroidal Anti-Inflanatory Drugs (NSAID)/opioids consumption, improve recovery and reduce length of hospital stay. Various doses of Neostigmine (25 µg, 50 µg, 75 µg, 100 µg and 150 µg) have been studied as an adjuvant to intrathecal 15 mg of 0.5% hyperbaric Bupivacaine [5-7], and concluded that the analgesia effect and side effects are dose-related; and have recommended 50 µg as the better choice with the minimal side effect, stable haemodynamics and prolonged analgesia.

Fentanyl is a synthetic opioid related to phenylpiperidine compound: it has rapid onset and shorter duration of action due to its lipophilic nature than hydrophilic opioids [8]. The recommended intrathecal dose is 10 to 30 µg, and when used as an adjuvant, dose of local anaesthetic is reduced and has produced a synergistic potentiating effect with the advantage of better motor and analgesic effect [8, 9]. The glutamate and substance P, released from the primary sensory neuron in the substantia gelatinosa, are inhibited by opioids. Opioids also decrease their pain-induced release of tachykinin from the primary afferent nociceptors.

So, based on previous research work, the present study is undertaken to compare between Neostigmine (50 µg) and Fentanyl (30 µg) as an adjuvant to intrathecal hyperbaric Bupivacaine (15 mg) in regards to the mean time to onset of sensory and motor block, haemodynamic stability, postoperative analgesia and side effects.

MATERIALS AND METHODS

The present, prospective, hospital-based study was carried out in Assam Medical College and Hospital, Dibrugarh, Assam, during the period from June 2020 to May 2021, after obtaining approval from the Institutional Ethical Committee (IEC) and written informed consent from the patient. A randomized, single-blinded study involving 80 patients aged 18 to 60 y of either sex, ASA Physical Status I and II, scheduled for elective lower limb and lower abdominal surgeries under lumbar spinal anaesthesia were included in the study. Patient with contraindication to spinal anaesthesia, pregnant and lactating women, severe cardiovascular or renal or hepatic disability, allergic to Bupivacaine and study drugs, coagulopathy, spinal deformity or previous spine surgery were excluded from the study. A pre-operative evaluation of all patients was done during pre-anesthetic check-ups. A thorough history,

physical and clinical examination, and necessary laboratory investigation were done. The anaesthetic technique and Visual Analogue Scale (VAS) score to assess pain in the peri-operative period was explained to each patient. On the night before surgery, tablet Alprazolam 0.5 mg was given and advised nil per orally (NPO) as per ASA standards.

Study group

80 patients were randomly divided into two groups; each group consisting of 40 patients.

Group N: Received 0.5 % Hyperbaric Bupivacaine 03 ml (15 mg) with Neostigmine 50 µg (0.1 ml) and Normal Saline (0.5 ml).

Group F: Received 0.5% Hyperbaric Bupivacaine 03 ml (15 mg) with Fentanyl 30 µg (0.6 ml).

On arrival of the patient in the pre-operative room, an intravenous (IV) line was secured using an 18 Gauze (G) IV cannula and preloaded with Ringer's Lactate solution (10 ml/kg) before the commencement of the anaesthetic procedure. In the operation theatre, ASA standard monitors were attached [Non-Invasive Blood Pressure (NIBP), Electrocardiogram (ECG), Pulse oximeter]. All the baseline values were recorded.

Technique of anaesthesia

After proper positioning of the patient, under all aseptic and antiseptic precautions, a lumbar puncture was performed through a midline approach at either L_{2-3} or L_{3-4} intervertebral space by using a 25G Quincke's spinal needle. After the free flow of Cerebrospinal Fluid (CSF), the study drug was administered slowly at the rate of 0.2 ml/second into the intrathecal space. The time of intrathecal administration of the study drug was recorded as 0 min. The patient was then placed in the supine position. Every patient received Inj. Pantaprazole 40 mg and Injection Midazolam 01 mg as premedication, and oxygen supplementation were given with the aid of an oxygen face mask.

Data collection

- The onset and level of sensory block was assessed by Pinprick test by using 23G hypodermic needle after administration of the study drug till the desired peak level (T_6) was achieved. Time taken to achieve block to T_6 was recorded. Time taken for two-segment block regression was also noted.
- Time to achieve Modified Bromage Scale 3 (MBS-3) in the lower limb after administration of the study drug was taken as time to onset of motor block and recorded.
- Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate, Respiratory Rate and Oxygen Saturation (SpO_2) were recorded at every five minutes for first 15 min, then at every 15 min till the end of the surgery, and then during the postoperative period until the termination of the study. Any fall of Blood Pressure>20% of baseline or<90 mmHg was taken as hypotension. Heart rate<50 beat per minute (bpm) was taken as bradycardia.
- Visual Analogue Scale (VAS) score was recorded at 0 min, 30 min, 60 min and then at every 1 h interval until 24 h or till the requirement of first rescue analgesia (VAS≥4) during the post-operative period, whichever was the earlier.
- Duration of effective analgesia was recorded as time interval from the administration of intrathecal drug to first complain of pain (VAS≥4) during the post-operative period.
- Side effects like nausea, vomiting, pruritus, hypotension, bradycardia, etc., were recorded.

Table 1: Modified bromage scale (MBS)

Modified bromage scale
MBS-0: No motor block
MBS-1: Inability to raise extended leg; able to move knees and feet
MBS-2: Inability to raise extended leg and move knee; able to move feet
MBS-3: Complete block of motor limb

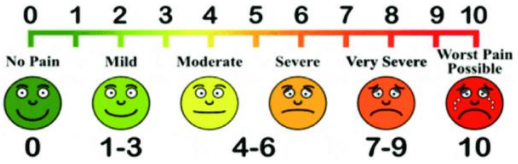

Fig. 1: Visual Analogue Scale (VAS) score

Statistical method

The statistical analysis of data collected was performed using the computer program Statistical Package for Social Science (SPSS for Windows, version 20.0. Chicago, SPSS Inc.) and Microsoft Excel 2010. Results on continuous measurements are presented as mean±standard deviation and are compared using student's t-test. Discrete data are expressed as number (%) and are analyzed using Fischer's exact test. For all analyses, the statistical significance was fixed at 5% (p-value<0.05).

RESULTS

The demographic variables like mean age, weight and height, ASA Physical Status, gender and duration of surgery in both the groups were comparable with no significant difference (p-value>0.05) (table 2).

The mean time to onset of sensory block in Group N and Group F was 93.43±8.49 seconds and 96.30±7.94 seconds, respectively. There was no significant difference (p-value = 0.1219) regarding the mean time to onset of sensory block in both groups (table 3).

The mean time to onset of peak sensory block (T_6) in Group N and Group F was 250.53±18.61 seconds and 252.30±15.37 seconds, respectively. There was no significant difference (p-value = 0.6431) in regard to mean time to onset of peak sensory block (T_6) in both groups (table 3).

The mean time to onset of motor block (MBS-3) in Group N and Group F was 426.63±29.19 seconds and 415.55±34.75 seconds, respectively. There was no significant difference (p-value = 0.1268) in regard to mean time to onset of motor block (MBS-3) in both the groups (table 3).

The mean time to two-segment block regression in Group N and Group F was 126.45±10.24 min and 93.43±8.49 min, respectively. It was observed that the mean time to two-segment block regression of Group N was slower than that of Group F, and on comparison, there was highly significant difference (p-value<0.0001) between the groups (table 3).

The mean time to first rescue analgesia in Group N and Group F was 476.45±30.94 min and 311.40±21.16 min respectively. It was observed that the mean time to first rescue analgesia of Group N was delayed than that of Group F, and on comparison, there was highly significant difference (p-value<0.0001) between the groups (table 3).

During the post-operative period, the first rescue analgesia was given when the VAS score was ≥4. The VAS score at 30 min in Group N is 0.50 ± 0.43 and 0.63±0.54 in Group N and Group F, respectively, with no significant difference (p-value = 0.0898). However, during the post-operative period, the VAS score at 60 min was 0.93±0.42 and 1.83±0.64, at 02 h was 1.28±0.45 and 2.73±0.60; and at 03 h was 1.73±0.72 and 3.53±0.51 in Group N and Group F, respectively, with highly significant difference (p-value<0.0001) on comparison between the groups (table 4). The VAS score at 04 h, 05 h and 06 h after the completion of surgery was 2.13±0.72, 2.85±0.62 and 3.73±0.45, respectively, in Group N.

The haemodynamic profiles including the mean heart rate, mean systolic and diastolic pressure, oxygen saturation (SpO_2) and respiratory rate, were comparable in both the groups with no significant difference between the groups on comparison (p-value>0.05).

In the present study, 09 patients had nausea and 07 patients had vomiting in Group N, whereas only 02 patients had nausea and 01 patient had vomiting in Group F, which on comparison had significant difference (p-value<0.05) between the groups (table 5). However, 01 patient in Group N and 04 patients in Group F had

developed hypotension, 01 patient in Group N and 02 patients in Group F had developed bradycardia, and 01 patient in Group N and 02 patients in Group F had developed shivering with no significant difference (p-value>0.05) in between the groups. Other side effects like pruritus, sedation, ventilatory depression and bronchospasm, were not seen in both the groups.

Table 2: Demographic profile

Duration		Group N	Group F	p-value
		Mean±SD	Mean±SD	
Age (years)		37.53±12.23	40.95±12.61	0.2210
Height (cm)		163.88±6.43	165.20±5.06	0.3085
Weight (kg)		56.08±3.27	54.65±4.73	0.1214
Gender	Male	13	16	0.6420
	Female	27	24	
ASA physical	I	29	24	0.3444
status	II	11	16	
Duration of surgery (min)		91.50±15.46	87.33±14.74	0.2200

Table 3: Characteristics of spinal anaesthesia

Duration	Group N	Group F	p-value
	Mean±SD	Mean±SD	
Mean time to onset of sensory block (sec)	93.43±8.49	96.30±7.94	0.1219
Mean time to onset of peak sensory block (T6) (sec)	250.53±18.61	252.30±15.37	0.6431
Mean time to onset of motor block (MBS-3) (sec)	426.63±29.19	415.55±34.75	0.1268
Mean time to two-segment block regression (min)	126.45±10.24	93.43±8.49	0.0001
Mean time to first rescue analgesia (VAS>4) (min)	476.15±30.94	311.40±21.16	0.0001

Table 4: Visual Analogue Scale (VAS) score during the post-operative period

Time	Group N	Group F	
	Mean±SD	Mean±SD	p-value
0	0	0	0
30 min	0.50±0.43	0.63±0.54	0.0898
60 min	0.93±0.42	1.83±0.64	0.0001
02 hour	1.28±0.45	2.73±0.60	0.0001
03 hour	1.73±0.72	3.53±0.51	0.0001
04 hour	2.13±0.72	-	
05 hour	2.85±0.62	-	
06 hour	3.73±0.45	-	

Table 5: Side effects

Side effects	Group N	Group F	p-value
	Number (%)	Number (%)	
Nausea	09 (22.5)	02 (5.0)	0.0229
Vomiting	07 (17.5)	01 (2.5)	0.0253
Hypotension	01 (2.5)	04 (10.0)	0.1700
Bradycardia	01 (2.5)	02 (5.0)	0.5620
Shivering	01 (2.5)	02 (5.0)	0.5620
Pruritus	0	0	0
Sedation	0	0	0
Ventilatory Depression	0	0	0
Bronchospasm	0	0	0

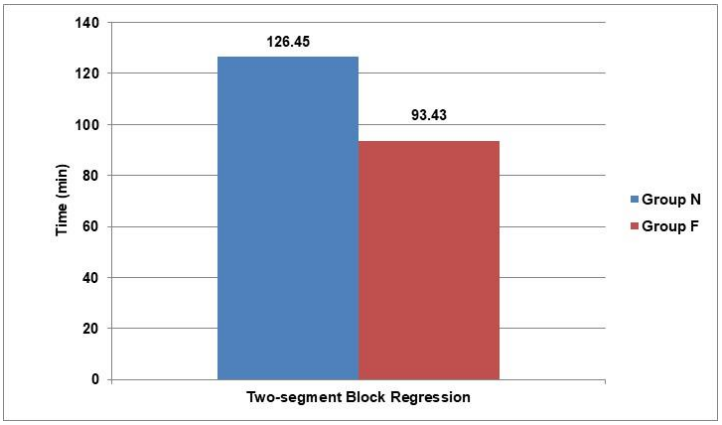

Fig. 2: Two-segment block regression

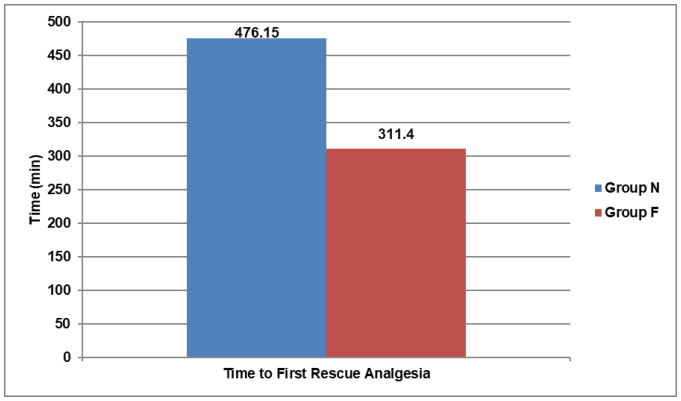

Fig. 3: Time to first rescue analgesia

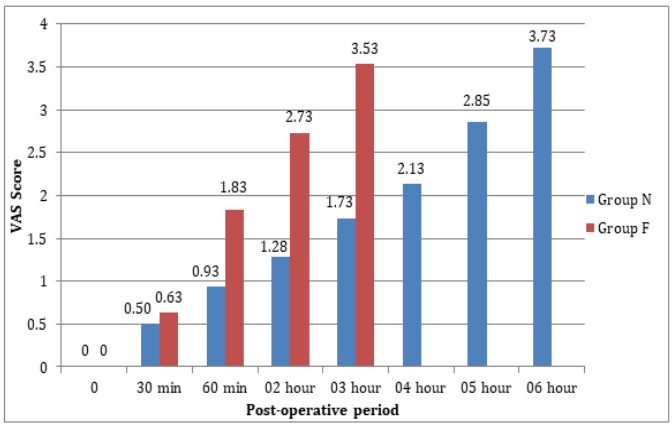

Fig. 4: Visual Analogue Scale (VAS) score during post-operative period

DISCUSSION

Nociceptive surgical stimuli result in acute pain and lead to sensitization of peripheral and central pathways. Though pain is personalized to each patient and is influenced by biological response, psychological state, etc.; thus having multifactorial etiology, its prevention is the responsibility of the anaesthesiologist. Poorly controlled acute post-operative pain is a predictive factor of Chronic Persistent Post-Surgical Pain (CPSP). Effective analgesia in the early post-operative period facilitates short and long-term recovery and quality of life.

Local anaesthetics in combination with adjuvants enhance the onset, improve the quality and prolong the duration of subarachnoid block: so, better pain relief in the immediate postoperative period. In the present study, it has been shown that intrathecal use of either 50 µg of Neostigmine [5, 10, 11] or 30 µg of Fentanyl [12-14] in combination with 0.5% hyperbaric Bupivacaine produces effective analgesia and anaesthesia. The outcomes like the time to both motor and sensory block did not differ between the groups (p-value>0.05).

The mean time to onset of sensory block in Group N was 01 minute 33 seconds approximately (approx.) in the present study and it was in concurrence with the previous studies on intrathecal Neogstimine by Ruparel DH *et al.* [7], Bhaskar HU *et al.* [11] and Yoganarashima N *et al.* [15]. Also, the mean time to onset of sensory block in Group F was 01 minute 36 seconds (approx.) and was similar to the studies on intrathecal Fentanyl by Dalvi NP *et al.* [16] and Nahakpam S *et al.* [17].

On the other hand, the mean time to onset of peak sensory block (T_6) in Group N was 04 min 10 seconds (approx.) and it correlated to the study on intrathecal Neostigmine done by Shakya ML *et al.* [10] and Bhaskar HU *et al.* [11]. Similarly, the mean time to onset of peak sensory block (T_6) in Group F was 04 min 12 seconds (approx.) and it correlated to the study on intrathecal Fentanyl done by Shakya ML *et al.* [10] and Nahakpam S *et al.* [17].

Similarly, the mean time to onset of motor block (MBS-3) in Group N and Group F was 07 min 06 sec and 06 min 55 sec respectively. This correlated to the study of Shakya ML *et al.* [10]. This observation demonstrated that both intrathecal Neostigmine and Fentanyl enhance the motor block in spinal anaesthesia also.

In the present study, the two-segment block regression was significantly faster in Group F on comparison to Group N (p-value<0.05). The mean time to two-segment block regression in Group N was 02 hours 06 minutes (approx.) and in Group F was 01 hour 33 minutes (approx.) which correlated to the study conducted by Bhaskar HU et al (11) and Seewal R et al (14), respectively. Previous studies reported that both intrathecal Neostigmine and Fentanyl delay spinal block regression more than Bupivacaine alone [18, 19].

The intrathecal neostigmine mediates the anti-nociception through the muscarinic receptors present in the spinal cord. It inhibits the AchE and, thereby, increases the concentration of Ach, which in turn produces the analgesia. Intrathecal fentanyl which is lipophilic, acts on the mu opioid receptors present on the dorsal horn of the spinal cord, thereby causing alteration of pain perception and producing intense analgesia. Both intrathecal Fentanyl [14] and Neostigmine [7] in combination with hyperbaric Bupivacaine in spinal anaesthesia have produced a longer duration of analgesia than that of the Bupivacaine alone.

However, the present study demonstrated that the duration of analgesia provided by intrathecal Neostimine was significantly longer than that of intrathecal Fentanyl. Therefore, the overall VAS score in those patients receiving the intrathecal Neostigmine was lesser during the post-operative period. It was similar to the study by Pandey V *et al.* [6] and Moges K *et al.* [20]. Hence, the time to the demand of the first rescue analgesia by the patients was prolonged in those patients receiving the intrathecal Neostigmine [07 h 56 min (approx.) in Group N and 05 h 11 min (approx.) in Group F in the present study, p-value<0.0001]. Lauretti GR *et al.* [21] demonstrated

that IV Morphine requirement was after 08 h post-operatively following the use of intrathecal Neostigmine. It correlated with the previous studies done by Shakya ML *et al.* [10], Seewal R *et al.* [14] and Farzi F *et al.* [22].

The high lipid solubility of intrathecal Fentanyl is responsible for its rapid clearance from Cerebrospinal Fluid (CSF), thereby causing a lesser cephalic spread and hence, fewer side effects [23-25] with the use of intrathecal Fentanyl. However, nausea and vomiting were severe in those patients receiving intrathecal Neostigmine, requiring prompt treatment with antiemetic and prokinetics. Neostigmine can easily spread into the supraspinal level [7, 26] when administered intrathecally, leading to the accumulation of Ach at brain stem and stimulation of Chemoreceptor Trigger Zone (CTZ); thereby causing a dose-dependent higher incidence of nausea and vomiting. In the present study, incidence of nausea and vomiting was significantly different between the groups (p-value<0.05); similar results were observed in the study of Ruparel DH *et al.* [7] and Shakya ML *et al.* [10]. Regarding haemodynamic stability, the incidence of hypotension and bradycardia was lesser in Group N than in Group F, but with no significant differences between the groups (p-value>0.05). Shivering was also observed in both groups and was insignificant (p-value>0.05). However, other side effects like pruritus, sedation, ventilatory depression and bronchospasm were not seen in both groups.

CONCLUSION

Both Neostigmine and Fentanyl can be considered as safe and effective adjuvant to Bupavacaine in spinal anaesthesia for lower limb and lower abdominal surgeries; both having the advantages of providing good analgesia and haemodynamic stability with minimal side effects. Neostigmine is superior to Fentanyl in regards to prolongation of post-operative analgesic effect. However, nausea and vomiting limits the use of intrathecal Neostigmine as an adjuvant to hyperbaric Bupivacaine for spinal anaesthesia.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

There is no conflict of interest

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