Original Article

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Comparative Efficacy of Addition of Fentanyl and Neostigmine to Isobaric 0.75% Ropivacaine in Elderly Patients undergoing Transurethral Resection of Prostate under Spinal Anaesthesia: A Double-blinded Randomised Clinical Study

PRAGYA SHUKLA[1], SANDEEP LOHA[2], RAVI KUMAR VERMA[3]

ABSTRACT

Introduction: Ropivacaine is a well-accepted local anaesthetic drug used in spinal and peripheral nerve blocks. It provides a better Central Nervous System (CNS) and cardiovascular stability in comparison to bupivacaine. Adjuvants are also added with these drugs as they provide haemodynamic stability, increase efficacy, and decrease the dose requirement of the local anaesthetic drugs.

Aim: To determine the efficacy of isobaric 0.75% ropivacaine in combination with normal saline, fentanyl, and neostigmine in Elderly Patients Undergoing Transurethral Resection of Prostate Under Spinal Anaesthesia.

Materials and Methods: This double-blinded randomised clinical study was conducted in the Department of Anaesthesiology and Critical Care, Institute of Medical Sciences-Banaras Hindu University, Varanasi, Uttar Pradesh, India, from July 2018 to June 2019. The study included 90 patients who were divided into three groups of 30 subjects each. Ropivacaine combined with normal saline in group RNS, ropivacaine combined with fentanyl in group RFE and ropivacaine combined with neostigmine in group RNE, was administered intrathecally. Heart rate, respiratory rate, blood pressure, onset and duration of sensory and motor block, along with the duration of analgesia, were recorded at different time points. The Analysis of Variance (ANOVA) was used to compare the variables among the three study groups, and Student-Newman-Keuls post hoc test was used to compare the data between the groups.

Results: Patients in group RNE showed a significant fall in heart rate in comparison to groups RNS and RFE at all the time points. Respiratory rate followed a similar pattern in group RNE ($p<0.001$), except at 5 min and 90 min. Mean systolic blood pressure showed a significant rise in group RNE compared to the other two groups, while diastolic blood pressure followed a similar trend at 10, 20, 30, and 60 min. The SpO_2 (%) was comparable among groups. The onset of sensory loss was significantly earlier in group RNE (239.6±28.8 sec) than in groups RNS (298.1±27.8 sec), and RFE (261.9±32.2 sec). The duration of the sensory block was significantly longer in group RFE (227.8±30.5 min). The mean time to the onset of motor block (480.7±30.2 sec) and analgesia (582.33±30.2 min) was longer in group RNE than in other groups.

Conclusion: The addition of neostigmine to ropivacaine intrathecally is a reliable method to prolong spinal anaesthesia but close monitoring of vitals is desirable.

Keywords: Analgesia, Intrathecal, Motor, Sensory

INTRODUCTION

Spinal anaesthesia is the most convenient anaesthetic technique used in surgery below the umbilicus. Its advantages over General Anaesthesia (GA) are reduced stress response, rapidity in onset, postoperative pain relief, shorter hospital stay, and cost-effectiveness. It is generally performed by using local anaesthetic drugs at different doses and baricity with or without the addition of an adjuvant. These adjuvants provide haemodynamic stability and decrease the dose requirement of the local anaesthetic drugs.The most commonly used local anaesthetic drug is bupivacaine. However, ropivacaine is also well accepted currently in spinal and peripheral nerve blocks, providing better Central Nervous System (CNS) and cardiovascular stability in comparison to bupivacaine [1,2]. As ropivacaine is approximately 40% less powerful than bupivacaine, it can be utilised for brief length surgeries [3].

Isobaric ropivacaine provides a similar sensory but shorter duration of the motor block with better haemodynamic stability compared to bupivacaine, and it is a desirable feature for early ambulation, voiding, and physiotherapy [4]. Luck JF et al., compared the same doses of hyperbaric ropivacaine, bupivacaine, and levobupivacaine intrathecally and concluded that ropivacaine may be useful when prompt mobilisation is required [5].

Intrathecal opioids as an adjuvant act synergistically with local anaesthetic drugs to intensify sensory block while achieving a satisfactory quality of spinal anaesthesia at a much lower dose of local anaesthetic drugs [6,7]. Fentanyl is a commonly used centrally acting opioid that is usually combined with the local anaesthetic agent for perioperative anaesthesia and analgesia [6]. Neostigmine is an adjuvant that causes analgesia by muscarinic receptor-mediated mechanisms. Neostigmine given intrathecally alone produces analgesia in humans at doses greater than 100 mcg [8-10]. Dose of 25 mcg would be unlikely to cause side-effects and has produced evidence of analgesia in clinical trials [8,9].

This study was conducted to observe the comparative efficacy of intrathecal administration of isobaric 0.75% ropivacaine in combination with normal saline as control, with fentanyl, and with

neostigmine as adjuvants in relation to their effects on the duration of analgesia as a primary outcome. Vital parameters, onset, and duration of sensory and motor blockade were also recorded as a secondary outcome in patients with benign prostatic hypertrophy undergoing Transurethral Resection of the Prostate (TURP).

MATERIALS AND METHODS

This double-blinded randomised clinical study was conducted in the Department of Anaesthesiology and Critical Care, Institute of Medical Sciences-Banaras Hindu University, Varanasi, Uttar Pradesh, India, from July 2018 to June 2019. The study protocol was approved by Institutional Ethical Committee (Dean/2018/EC/460) and written informed consent was obtained from all patients. The study was conducted in 90 adult patients, scheduled for TURP under spinal anaesthesia.

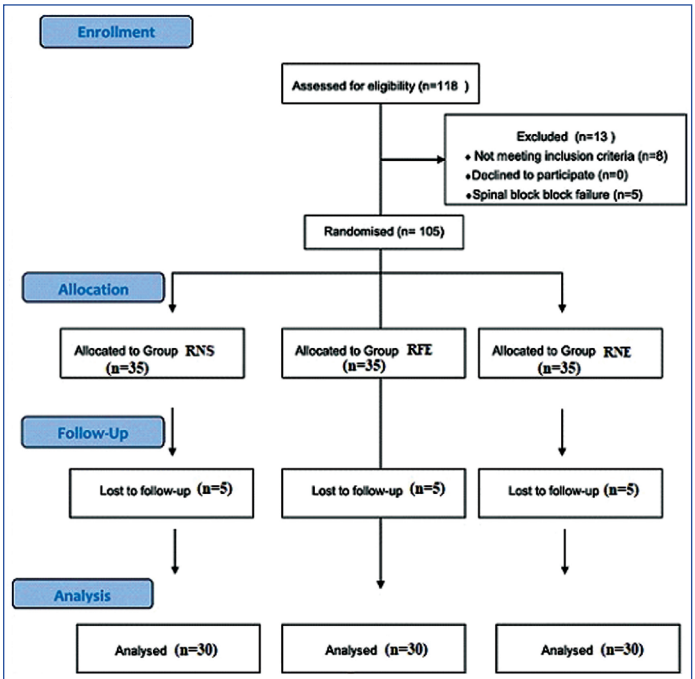
Inclusion criteria: Patients of age group 45-65 years, grades I and II prostratomegaly [11], American Society of Anaesthesiologists (ASA) grade I and II scheduled for elective TURP were included in the study.

Exclusion criteria: Patients, with CNS infections, progressive neurodegenerative disorders, severe cardiopulmonary disease, blood volume deficits, bleeding diathesis and coagulopathy, local infection and spine deformities, allergy to local anaesthetics and opioids and those who did not give consent were excluded from the study.

Sample size calculation: With α=5% (level of significance of two-tailed test), β=0.1 (90% is the power of the study with one-to-one ratio), δ=8.5 (mean difference) and σ=10 minutes (standard deviation), the sample size was calculated using the formula [12]:

$$2N=\frac{4(Z\alpha+A\beta)^2\sigma^2}{\delta^2}$$

The final sample size for each group was found to be 30. Patients were randomly allocated through a computer-generated random table number to the following groups [Table/Fig-1].



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Group RNS: Received 18.75 mg (2.5 mL) of ropivacaine 0.75% with (0.5 mL) normal saline intrathecally.

Group RFE: Received 18.75 mg (2.5 mL) ropivacaine 0.75% with 25 µg (0.5 mL) fentanyl intrathecally.

Group RNE: Received 18.75 mg (2.5 mL) ropivacaine 0.75% with 25 µg (0.5 mL) neostigmine intrathecally.

Study Procedure

All patients received tab. alprazolam 0.25 mg, tab. ranitidine 150 mg and tab. metoclopramide 10 mg on the night before surgery and 2 hrs before surgery as preanaesthetic medication. Before arriving in the Operation Theatre (OT), 5 mL/kg of 0.9% normal saline was given intravenously to all patients. The monitors were attached to the patients to record baseline vitals, i.e., heart rate, respiratory rate, non invasive blood pressure, and oxygen saturation (SpO_2) before initiation of spinal anaesthesia.

In all groups, spinal anaesthesia was induced in the lateral decubitus position either at L2-3 or L3-4 interspace using 25 gauge Quincke's type of spinal needle and the study medication was administered within 30 seconds into the subarachnoid space with aseptic precautions. The patients were then positioned in a supine position without head elevation. The T10 dermatome levels were targeted for the spinal block. All patients were given supplemental oxygen via a venti-mask at a rate of 5L/min throughout the operation.

Sensory block: Loss of sensation to pinprick bilaterally was determined with a blunt 27-gauge needle by a blind observer. Time to achieve the T10 dermatome level was noted.

Motor block: The level of motor blockade was assessed by the Bromage scale:

0- no motor block

1- not able to raise extended legs

2- not able to flex knees but able to move feet

3- not able to flex ankle joints

The patients were asked to move the extended legs, and when they were not able to lift them, the time was recorded, and also the resolution times of sensory and motor blockade were recorded.

Heart rate, respiratory rate, blood pressure, and SpO_2 (%) were recorded at 1, 5, 10, 20, 30, 60, 90, and 120 min. Hypotension was defined as a decrease of more than 20% from the baseline systolic blood pressure and was treated with an intravenous (IV) bolus of 5 mg ephedrine, repeated every 3 min. Bradycardia was defined as the heart rate <40 beats per min and was treated with 0.5-1 mg of IV injection of atropin. The duration of analgesia was recorded by asking the patient about the onset of pain and for postoperative pain relief, a 75 mg Intramuscular (IM) injection of diclofenac sodium was given when required (first analgesic requirement). The study ended at the 24th hr after all data had been recorded.

STATISTICAL ANALYSIS

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 20.0 software version. The mean and standard deviation were calculated for different parameters. The Analysis of Variance (ANOVA) was used to compare the variables among the three study groups, and Student-Newman-Keuls post hoc test was used to compare the data between the groups. A p-value <0.001 was considered to be highly statistically significant and p<0.05 was significant.

RESULTS

The patients in all three groups were comparable for demographic data in terms of age, weight, height, and ASA grading [Table/Fig-2]. Comparison of the the mean heart rates and respiratory rates at different time points are presented in [Table/Fig-3] and [Table/Fig-4], respectively. The patients of group RNE showed a significant fall in heart rate in comparison to groups RNS and RFE, at all time points [Table/Fig-3]. The respiratory rate also followed a similar pattern to heart rate in group RNE, at different time points (p<0.001), except at 5 min and 90 min [Table/Fig-4].

Comparisons of mean systolic and diastolic blood pressure among the three groups are presented in [Table/Fig-5,6], respectively. Mean systolic blood pressure showed a significant rise at all time points in group RNE when compared with group RNS and group RFE.

Parameters	Group RNS (Mean±SD)	Group RFE (Mean±SD)	Group RNE (Mean±SD)
Age (years)	59.5±6.1	57.8±5.6	59.4±5.7
Weight (kg)	69.5±6.3	67.2±5.9	69.1±7.3
Height (cm)	165.6±6.6	165±6.6	165±6.4
Prostratomegaly Grade I/II (n)	23/7	23/7	20/10
ASA Grade I/II (n)	19/11	20/10	19/11

[Table/Fig-2]: Basic demographic profile of study groups.

Heart rate (per min)	Group RNS (Mean±SD)	Group RFE (Mean±SD)	Group RNE (Mean±SD)	p-value (ANOVA)
Preoperative	82.731±15.5	83.03±13.0	72.7±13.8	<0.01
1 min	82.50±18.2	85.3±11.9	66.6±17.1	<0.001
5 min	84.26±21.8	80.26±10.6	65.26±14.3	<0.001
10 min	81.33±17.2	82.33±12.1	63.63±14.2	<0.001
20 min	76.80±20.8	81.0±11.3	63.90±13.8	<0.001
30 min	77.06±16.9	75.66±10.6	61.03±11.9	<0.001
60 min	78.60±20.6	75.86±13.0	66.43±12.50	<0.05
90 min	75.10±13.8	73.70±11.7	64.70±10.0	<0.01
120 min	78.66±18.5	79.06±12.4	63.20±11.7	<0.001

[Table/Fig-3]: Comparison of heart rate at different time points (mean±SD).

Respiratory rate (per min)	Group RNS (Mean±SD)	Group RFE (Mean±SD)	Group RNE (Mean±SD)	p-value (ANOVA)
Preoperative	13.40±1.5	15.03±1.6	12.86±1.0	<0.001
1 min	13.70±1.2	15.13±1.4	13.0±0.8	<0.001
5 min	17.26±18.5	14.53±1.1	13.43±0.6	0.367
10 min	14.53±1.5	14.60±1.2	12.80±0.8	<0.001
120 min	13.90±1.3	14.90±1.2	13.40±1.0	<0.001
30 min	14.63±1.3	14.80±1.4	13.16±1.0	<0.001
60 min	14.53±1.3	15.03±1.6	13.50±1.0	<0.001
90 min	14.33±1.0	21.60±25.1	13.56±1.0	0.067
120 min	14.33±1.0	14.66±1.2	13.43±1.0	<0.001

[Table/Fig-4]: Comparison of respiratory rate at different time points (mean±SD).

Systolic BP (mmHg)	Group RNS (Mean±SD)	Group RFE (Mean±SD)	Group RNE (Mean±SD)	p-value (ANOVA)
Preoperative	130.26±10.1	115.80±12.8	129.53±9.3	<0.001
1 min	128.60±17.0	117.93±12.0	133.73±9.5	<0.001
5 min	116.20±7.4	119.13±11.3	133.0±10.3	<0.001
10 min	115.86±14.2	122.40±8.3	131.60±10.3	<0.001
20 min	114.93±12.8	122.50±10.1	135.33±10.1	<0.001
30 min	117.06±8.4	120.46±9.4	132.46±13.5	<0.001
60 min	112.86±10.1	114.46±14.4	133.33±12.5	<0.001
90 min	116.33±8.4	114.53±13.3	131.73±8.3	<0.001
120 min	118.40±9.4	117.66±13.4	127.80±11.2	<0.01

[Table/Fig-5]: Comparison of systolic blood pressure at different time points (mean±SD).

Mean diastolic blood pressure was significantly higher in group RNE compared to group RNS and group RFE at 10, 20, 30, and 60 min of the observation period. However, it showed recovery and became comparable to that of group RNS and group RFE at 90 and 120 min. Moreover, the mean oxygen saturation percentage was almost similar in all three groups.

Mean onset of sensory loss (onset time of T10 level sensorial blockade) was significantly earlier in group RNE (239.6±28.8 sec) when compared to group RNS (298.1±27.8 sec) and group RFE (261.9±32.2 sec) (p<0.001). Whereas, the mean duration of sensory loss (at T10 level) was significantly prolonged in group RFE (227.8±30.5 min) when compared to group RNS (207.8±28.8 min, p<0.05), but comparable to group RNE (219.1±29.5 min). Mean time to onset of motor (Bromage score to become 3) was significantly earlier in group RNE (480.7±30.2 sec) when compared with group RNS (623.1±40.9 sec) and group RFE (597.9±32.1 sec) (p<0.001). The duration of motor blockade (Bromage score to become 0) was significantly prolonged in group RFE (244.7±28.3 min) and RNE (237.9±31.1 min), when compared with group RNS (202.3±30.7 min) (p<0.001) [Table/Fig-7].

Diastolic BP (mmHg)	Group RNS (Mean±SD)	Group RFE (Mean±SD)	Group RNE (Mean±SD)	p-value* (ANOVA)
Preoperative	79.93±11.50	77.30±13.0	74.66±7.0	0.177
1 min	76.73±10.3	73.86±10.1	79.2±5.4	0.075
5 min	79.53±9.7	76.33±8.0	75.53±7.6	0.05
10 min	72.26±9.3	73.86±5.8	78.53±8.6	0.010
20 min	71.20±11.9	74.46±6.8	77.7±7.1	0.022
30 min	71.26±8.4	72.73±5.6	76.33±8.2	0.032
60 min	71.46±8.8	69.13±11.6	76.80±7.4	0.008
90 min	73.53±8.3	71.60±9.7	76.40±6.9	0.091
120 min	74.86±6.1	74.13±10.3	75.40±9.60	0.858

[Table/Fig-6]: Comparison of diastolic blood pressure at different time points (mean±SD).

Parameters	Group RNS (Mean±SD)	Group RFE (Mean±SD)	Group RNE (Mean±SD)	p-value (ANOVA)
Onset of sensory loss (sec)	298.1±27.8	261.9±32.2	239.6±28.8	<0.001
Duration of sensory loss (min)	207.0±28.8	227.8±30.5	219.1±29.5	<0.05
Onset of motor blockade (sec)	623.1±40.9	597.9±32.1	480.7±30.2	<0.001
Duration of motor blockade (min)	202.3±30.7	244.7±28.3	237.9±31.1	<0.001
Duration of analgesia (min)	211.96±26.7	291.50±30.3	582.33±30.2	<0.001

[Table/Fig-7]: Characteristics of spinal block (mean±SD).

Duration of analgesia was significantly prolonged in group RNE (582.33±30.2 min) than group RNS (211.96±26.7 min) and group RFE (291.50±30.3 min). Furthermore, group RFE also had a significantly longer duration of analgesia than group RNS (p<0.001) [Table/Fig-7]. Various side-effects of drugs were noted during the observation period but were found to be non significant among the groups and are depicted in [Table/Fig-8].

Parameters	Group RNS n (%)	Group RFE n (%)	Group RNE n (%)
Nausea	2 (6.7)	3 (10)	7 (23.3)
Hypertension	4 (13.3)	0	2 (6.7)
Shivering	0	6 (20)	0

[Table/Fig-8]: Comparison of side-effects in the study groups (%).

DISCUSSION

The results of this study revealed that the mean duration of analgesia (first analgesia requirement time after the study drugs were given intrathecally) showed that it was significantly prolonged in group RNE than groups RNS and RFE (p<0.001). This is in accordance with the findings of Lauretti G et al., [13], Garg A et al., [14] and Shakya ML et al., [15], who also reported that the intrathecal neostigmine led to a prolonged duration of analgesia up to 12 hrs rather than intrathecal fentanyl. Pan PM and Mok MS, reported decreased requirement for other analgesics and provided longer postoperative analgesia with neostigmine compared to intrathecal fentanyl [16].

Furthermore, group RNS had a shorter duration of analgesia than group RFE. Chung CJ et al., showed that the addition of 10 µg fentanyl increases the duration of analgesia by approximately 40

min as compared to ropivacaine alone [17]. Sanli S et al., showed that addition of 10 µg fentanyl to 15 mg hyperbaric ropivacaine prolonged the duration of analgesia by approximately 24 min and the time to the rescue analgesic dose administration by approximately 52 min [18].

The mean time of onset of sensory loss in group RNE was significantly earlier when compared with groups RNS and RFE. Furthermore, in group RFE the onset of sensory loss was earlier when compared with group RNS. Shakya ML et al., reported that the mean onset of sensory loss with bupivacaine and neostigmine was earlier than bupivacaine with fentanyl [15]. McNamee DA et al., observed that onset, intensity, level, and duration had no significant differences in ropivacaine alone and in combination with fentanyl [19]. Whereas, a study conducted by Chaudhary A et al., which compared ropivacaine alone or in combination with fentanyl 10 µg, it was observed that there was no significant difference between the groups for the onset of sensory block at level T10 [20]. Luck JF et al., reported comparative analysis of bupivacaine, levobupivacaine, and ropivacaine and found no significant differences between the groups with regard to mean time to onset of sensory block at T10, extent of spread and mean time to maximum spread [5].

In the present study, the mean duration of sensory blockade was significantly longer in group RFE when compared with group RNS ($p<0.05$) which is similar to the study conducted by Gunaydin B and Tan ED, where they compared ropivacaine (15 mg) alone or in combination with fentanyl (20 µg) for the elective Caesarean section [21].

The mean time to onset of motor blockade (Bromage score to become 3) was significantly earlier in group RNE when compared with groups RNS and RFE. Whereas, duration of motor blockade (Bromage score to become 0) was significantly longer in groups RFE and RNE when compared with group RNS ($p<0.001$). Shakya ML et al., demonstrated that the mean onset of motor blockade was shorter in intrathecal neostigmine group than the fentanyl group [15]. Faiz SH et al., showed that the addition of neostigmine to bupivacaine significantly decreased the recovery time when compared with control group (125±27.4 vs 138.33±30.27 min) [12]. Thus, the combination of ropivacaine and neostigmine appears to be better in terms of onset and duration of motor blockade in patients with spinal anaesthesia for early ambulation surgeries.

On comparison of variations in mean heart rate at different time points, it was observed that group RNE showed a significant fall in heart rate in comparison to group RNS and RFE at all time points, whereas Shakya ML et al., found bradycardia in 0.03% of the patients on intrathecal administration of bupivacaine with neostigmine versus 0.13% in the bupivacaine with fentanyl group [15]. Pan PM and Mok MS [16] and Carp H et al., [22] reported a lesser incidence of bradycardia with intrathecal neostigmine than fentanyl, suggesting the more haemodynamic stable effect of neostigmine. In the present study, the respiratory rate also followed a similar pattern like heart rate for group RNE at different time points ($p<0.001$), except at 5 min and 90 min. Thus, one should have a close observation of the heart rate and respiratory rate of patients receiving neostigmine with anaesthetic medication during spinal anaesthesia.

The mean systolic BP was significantly lower in group RFE than groups RNS and RNE. It was further observed that in group RFE patients, systolic BP slightly increased after drug administration between 5 to 20 min, but settled to baseline at the end of 120 min. Furthermore, group RFE patients maintained their systolic BP, whereas, group RNS had a slight fall in their systolic BP after the drug was given intrathecally and was lower than the baseline throughout the procedure. Whereas, Shakya ML et al., found hypotension in 0.06% of cases receiving neostigmine and in 0.23% cases receiving fentanyl, and concluded that neostigmine maintains BP better in comparison to fentanyl [15]. Akhtar N et al., compared ropivacaine with the combination of ropivacaine with fentanyl and observed that mean heart rate and arterial pressure decreased significantly from their baseline values in both the groups [23].

When the groups were compared for variation in mean diastolic BP, it was again found significantly different in group RNE at 10, 20, 30, and 60 min from groups RNS and RFE. There was a rise in diastolic BP at the above time points, but later it returned back to baseline. Incidence of hypotension was lesser with neostigmine than fentanyl, suggesting a more haemodynamic stable property of neostigmine as reported by other authors [16,22]. Again, one should be careful about BP changes while using neostigmine as it increases the incidence of hypotension that can be managed with routine clinical measures. Moreover, the mean oxygen saturation percentage was almost similar in all three groups.

Side-effects like nausea, vomiting, bradycardia, hypertension, and shivering were observed. Nausea was the most common side effect in all three groups, especially in the neostigmine group. Shakya ML et al., reported that the incidence of nausea and vomiting was higher in the case of intrathecal neostigmine [15]. The rostral spread of neostigmine to the brainstem has contributed to the severity of these side-effects. Nausea as a common side effect of neostigmine limits its use, but with premedication like antiemetics, it can be easily controlled. Lauretti G et al., showed a dose-independent reduction of postoperative analgesia requirements, but a dose-dependent increase in the incidence of postoperative nausea and vomiting following the addition of various doses of intrathecally administered neostigmine (ranging from 25 to 100 µg) to 15 mg of hyperbaric bupivacaine 0.5% [13].

Thus, the findings of the present study demonstrated that haemodynamic instability can occur in combination of ropivacaine with neostigmine in comparison to ropivacaine with fentanyl or with normal saline. However, the major advantage of ropivacaine with neostigmine is that there is an early loss of sensory and motor components with prolonged duration of sensory and motor loss along with the prolonged period of analgesia which provides better comfort to patients undergoing spinal anaesthesia.

Limitation(s)

Extreme caution is required while preparing the drug to prevent contamination. Also, in the present study, all patients were either ASA physical status I or II. Results cannot be generalised to ASA physical status III and IV patients.

CONCLUSION(S)

Although neostigmine had higher incidence of side-effects, especially nausea and bradycardia, most of the patients tolerated well. Therefore, it can be a good alternative as an adjuvant to ropivacaine in spinal anaesthesia in patients with benign prostate hypertrophy undergoing elective TURP under careful haemodynamic monitoring.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Anaesthesiology, Institute of Medical Sciences - Banaras Hindu University, Varanasi, Uttar Pradesh, India.
2. Associate Professor, Department of Anaesthesiology, Institute of Medical Sciences - Banaras Hindu University, Varanasi, Uttar Pradesh, India.
3. Professor, Department of Anaesthesiology, Institute of Medical Sciences - Banaras Hindu University, Varanasi, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Pragya Shukla,
C/o Dr. O.P. Mishra-154, Janki Nagar Bazardeeha, Varanasi, Uttar Pradesh, India.
E-mail: shukla.pragya0509@gmail.com

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