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Comparison of Fentanyl and Midazolam as Adjuvants to Low Dose Isobaric Ropivacaine for Spinal Anaesthesia for Transuretheral Resection of Prostate

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Abstract

Background: Spinal ropivacaine provides differential anaesthesia with a higher sensory than motor block and is less cardiotoxic than bupivacaine. Small doses of ropivacaine (10- 15 mg) require addition of neuraxial adjuvants to improve the quality of block and duration of analgesia without affecting motor blockade. We designed a randomised double blind study to compare fentanyl and midazolam as additives to spinal ropivacaine 0.5% for patients scheduled for transuretheral resection of prostate (TURP). *Methods:* Forty patients scheduled for TURP were randomly assigned to group F (13.5mg isobaric ropivacaine 0.5% with 25 ug fentanyl) and group M (13.5 mg isobaric ropivacaine 0.5% with 1 mg midazolam). Evaluation of the performance of block, haemodynamics and side effects were recorded. A Minitab macro for MINITAB® Release 14.13 was used for pair-wise comparisons. Friedman's Test was applied to estimate statistical significance. A P value ≤ 0.05 was considered significant. *Results:* The changes in heart rate, systolic and diastolic blood pressures were not found to significantly differ between the groups but intragroup differences were statistically very significant in both groups. The time to onset of block was same in both groups but midazolam(15min) took a longer time to fix than fentanyl (10min). Subsequently, higher levels of block were noticed with midazolam. The time to achieve T10 block (P=0.93) and quality of motor block (P=0.81) were comparable between the two groups. *Conclusions:* Spinal anaesthesia with isobaric ropivacaine and fentanyl or midazolam provides an adequate sensory and motor blockade for elderly patients undergoing TURP.

Keywords: Anesthesia; Spinal; Fentanyl; Hypotension; Midazolam.

Introduction

Elderly males suffer with prostatic hypertrophy. TURP is performed under spinal anaesthesia to relieve the symptoms in majority of patients [1]. Bupivacaine is the most commonly used local anaesthetic. Elderly patients have age related cardiovascular compromise with 10% decrease per decade after 70 years of life. They are more prone for hypotension and bradycardia after regional block [2]. TURP require block upto T10 dermatome and good relaxation of lower limb muscles for maintaining lithotomy position. Low dose ropivacaine has advantage of a shorter duration of motor block which decreases the incidence of venous thromboembolism [3]. However, a shorter duration of sensory analgesia can increase the pain scores in immediate postoperative period. 0.75% ropivacaine is known to be associated with transient neurological symptoms [4].

Intrathecal fentanyl is a commonly used neuraxial adjuvant with pruritis as the most distressing symptom [5]. The mechanism of action with midazolam is by enhancement of GABA receptor activity [6]. Both these adjuvants have potential for sedation and respiratory depression at higher doses. We designed the present study to compare the block

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characteristics of low dose ropivacaine (13.5mg) with fentanyl and midazolam for TURP .

Methods

The study protocol was approved by the institutional ethics committee. Written and informed consent was obtained from all the patients enrolled for the study after explaining the anaesthetic procedure. All elderly men, classified as Grades I and II of American Society of Anesthesiology, posted for elective TURP surgery were enrolled in the study. Patients with absolute contraindications to spinal anaesthesia and allergic to study drugs were excluded.

Group F - had 20 patients who received 2.7ml of 0.5% ropivacaine (13.5 mg) with 25 ug fentanyl.

Group M -had 20 patients who received 2.7ml of 0.5% ropivacaine (13.5mg) with 1 mg midazolam.

0.5ml fentanyl (50 ug ml^{-1}) = ½ ml was used. Similarly, 1ml midazolam (5 ug ml^{-1}) was diluted in 2.5ml saline and a 0.5 ml of this was added to ropivacaine. This ensured that the total volume of injectate in both groups was 3.2ml.

Randomisation was achieved with 'sealed envelop' technique method. The drug was loaded aseptically in a 5 ml syringe by an anaesthesiologist not involved in statistical computation of results. The content of the syringe was disclosed to principal investigator at the end of surgery.

All patients were given tab alprazolam 0.25mg and tab Rantac 150mg night before and morning of surgery. Baseline heart rates, non invasive blood pressures and SpO_2 readings were recorded with Datex Ohmeda® monitor inbuilt in Aespire ®workstation (GE Healthcare,Chicago,USA). Intravenous access (IV) was established and ringer lactate was started.

A synthetic colloid Volulyte® (Fresenious kabi, Germany) was the second fluid to be infused under a standard protocol. The subarachnoid block is given to patient positioned sitting, in L3-L4 interspace with 27 guage quincke's spinal needle. The patient is made supine immediately after block. HR, SBP, DBP, SpO_2 were monitored every 1 min for initial 10 min and then at every 5 min interval till the end of surgery The sensory spread of block was assessed as loss of perception to cold (swab soaked with spirit) and pinprick (with a blunted 22g syringe needle). Modified Bromage score (1. No block, complete motor recovery 2. Able to flex knees, 3.Able to move toes and dorsiflex ankle 4. inability to raise extended leg and 5. A complete motor block) was used to document the motor block achieved.

Patients were positioned in lithotomy after 10 min and the surgery was started. O_2 was administered to all patients.

The haemodynamics, onset and duration of sensory and motor blockade, highest dermatomal level of sensory analgesia obtained and time to administer rescue analgesic in postoperative period was noted. Patients were observed for hypotension, pruritis, nausea, vomiting and sedation.(1. Alert to surroundings, 2. Asleep but arousable and 3. Deep asleep, no response to loud voice). Patients showing grade 3 sedation were urgently assessed for intubation needs to secure airway.

A SBP below 90 mmHg or a decrease of 20% of pre-block SBP was considered as hypotension. It was treated with IV mephentermine 6 mg. Vascular overhydration is expected with irrigation fluid absorbtion in this surgery. This can result in hypertension and cause increased blood loss. This affects the surgeon's endoscopic view. BP ≥ 150/100 were treated with 0.05 mg iv bolus of nitroglycerine. Atropine0.6 mg iv was administered if bradycardia occurred (defined as HR below 50 beats per min).

Statistical Methods

Calculation of sample size revealed that at least 15 subjects in each group were needed to detect a difference in the average time to rescue analgesics as small as 1.5 times its standard deviation with a power of 0.9 and a significance level (α) of 0.05 The sample size was increased by 30% (i.e. 20 patients in each group) as the distribution of the primary outcome variable (duration of analgesia) was expected to be skewed in a small sample of population.

The raw data was statistically analysed by MINITAB® Release 14.13, a minitab macro was developed for this pupose [7]. The continuous variables failed the normal distribution when assessed for skewness by Kolmogorov Smirnova test. Friedman's test i.e. non-parametric repeated measures analysis of variance (ANOVA) for HR, SBP, DBP and MAP separately for Fentanyl and Midazolam groups.

If found significant, pair-wise comparisons were done comparing with the baseline value. A P value d 0.05 was considered significant.

Results

Both groups were comparable in demographic profile, incidence of associated medical illnesses and duration of procedure (Table1). 5 patients were on antiplatelets and American society of regional anesthesia (ASRA) guidelines were followed before placing the block.

The onset of sensory analgesia was similar in both groups (2 min). The progression of block was faster in fentanyl group whereas higher blocks were achieved in patients who received midazolam. (P=0.02). The maximum block height was seen in midazolam (T4) in five patients (Table 2). Figure 1 shows the Kaplan myier analysis of the progression of block.

The HR in both the groups decreased by 8 -15% gradually after institution of SAB. The onset of decrease was noticed earlier with fentanyl than midazolam (5 versus 10min). Atropine was required in 4 patients (20%) in fentanyl group. Both groups showed an equal decrease in SBP from 6 min after the block which was found to be statistically significant in post hoc comparisons after Friedman test. 2 patients of midazolam group required a single small dose (6mg) of mephentermine IV. Nitroglycerine IV was used in 6(30%) patients in fentanyl group and 4(20%) patients in midazolam group. The diastolic pressures decreased in both the groups. Patients who received fentanyl exhibited an earlier onset of decrease in the pressures as compared to midazolam.(6 versus 9 min). The decrease in MAP was observed from 3 min interval in both the groups (P=0.05).

The regression of sensory analgesia to S1 was noted at 163.56± 21.44 min in fentanyl group and 189.0± 20.98 min in midazolam group of patients (P=0.05). Postoperative, recovery of motor power was achieved earlier in fentanyl group (52 ± 10.06 mins) than in the midazolam group (65 ± 12.10 mins).

The incidence of nausea and vomiting was comparable in both groups. None of the patient reported pruritis in postoperative period with fentanyl. 4 patients in midazolam group had sedation score of 3. They maintained SpO_2 above 95% with a nonobstructed airway throughout surgery. Their electrolytes and airway was monitored in the postoperative ward.

Table 1: Patient charactreistics

Parameters	Group F	Group M	P value
Age in years , mean ± SD	65± 1.26	64± 1.08	0.86
Duration in min, mean ± SD	94± 5.61	92± 4.82	0.24
Stable Coronary artery disease on medical disease	04	01	-
Controlled Hypertension	08	06	-
Controlled Diabetes	07	09	-
Chronic obstructive Lung disease	02	00	-
Previous Stroke	01	00	-

Fig. 1:

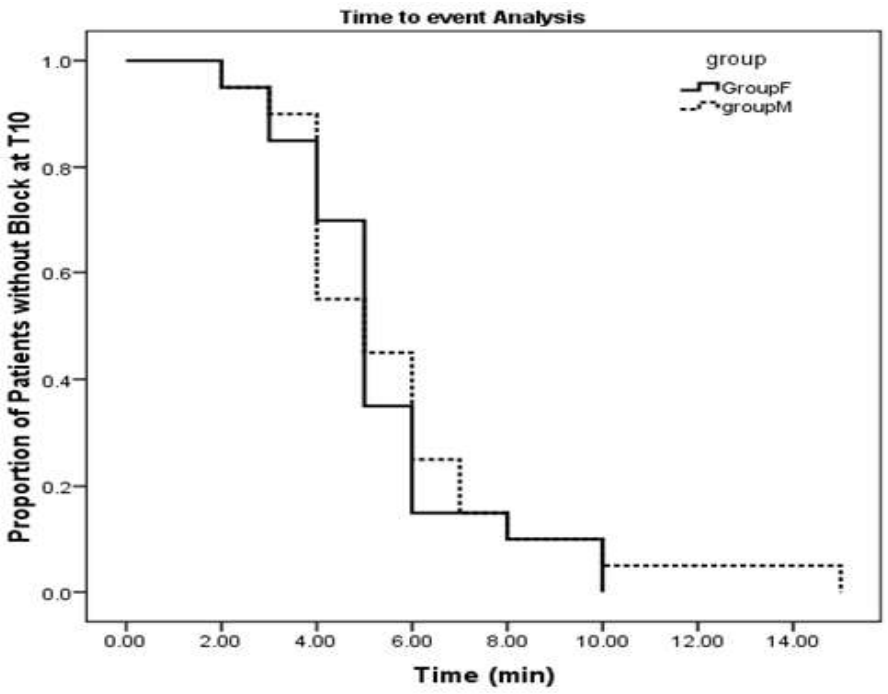


Table 2: Block characteristics

Parameter	Group F	Group M	P (Mann-Whitney test)
Time to T10 (median time in min)	5	5	0.9341
Time to achieve motor score of 5(median time in min)	6	7	0.8164
Progression of block			
@ 2 min, number of patients < T12	12	15	0.040
@ 5 min, number of patients <T10	6	9	0.038
@7 min, number of patients < T8	7	9	0.301
@10 min, number of patients<T6	8	7	0.182
@15 min, number of patients < T4	20	15	0.0012

Fig. 2:

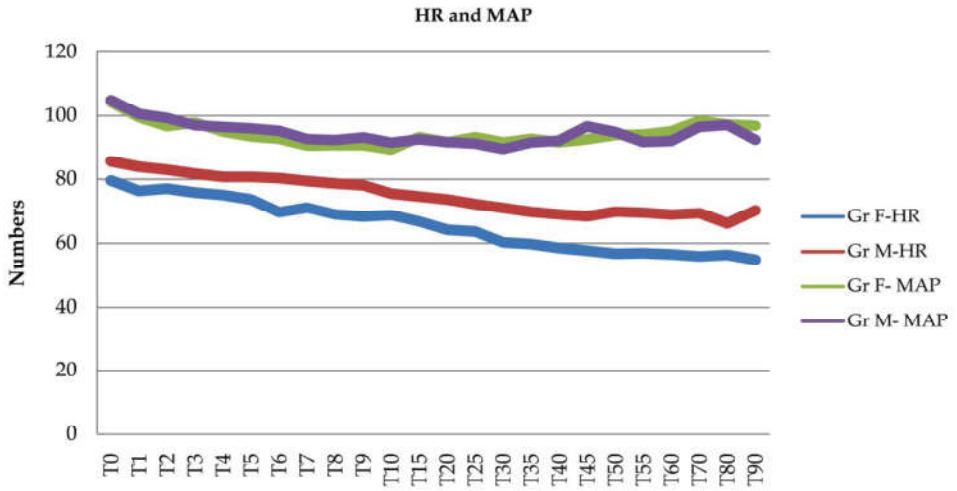
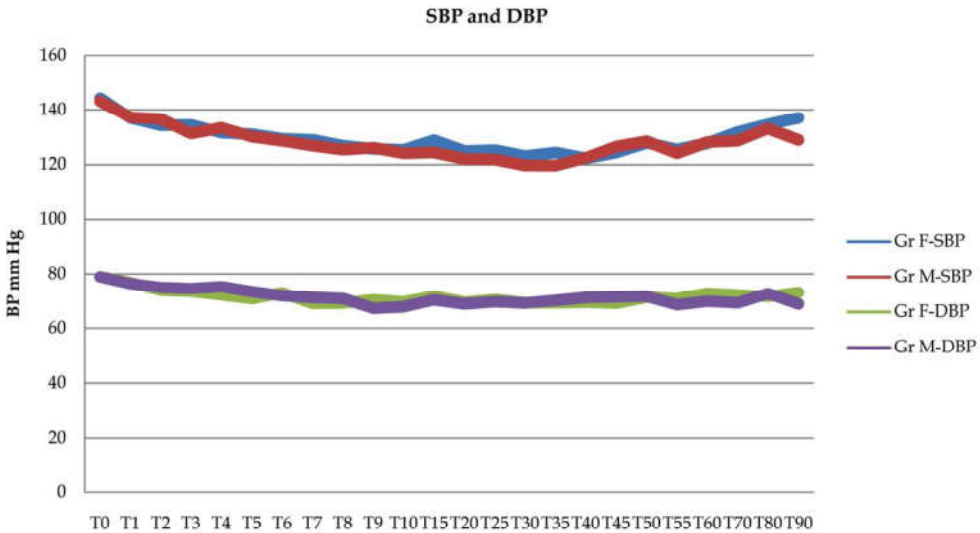


Fig. 3:



Discussion

Ropivacaine is a safe local anaesthetic for geriatric population. Malinovsky et al had found 16% of spinal anaesthetics from plain ropivacaine 15mg was inadequate for urological surgery [8]. In our study, we achieved a decrease in the duration of motor blockade with an exaggerated sensory analgesia with neuraxial adjuvants. Prolonged postoperative analgesia is beneficial after TURP as patients complain of pain from detruser muscle spasm. The spread of isobaric ropivacaine is dependent on the current produced by injection and simple diffusion so that the drug, which we inject through intrathecal route stays locally at the point of injection [9]. The higher block levels observed in our study can be explained by the isobaric nature of the drug which becomes further hypobaric on addition of spinal adjuvants.

The addition of opioids to spinal solutions is a common practice [10]. Yegin et al have concluded that 25 ug fentanyl added to 18 mg ropivacaine significantly improved the quality and prolonged analgesia without causing a substantial increase in the frequency of major side effects [11]. Benzodiazepines like midazolam have previously been studied in doses of 1-2 mg for potentiation of spinal anesthesia. Bupivacaine was the local anaesthetic used in those studies [12,13].

Lower heart rates seen in the fentanyl group can be an opioid related side effect. Fentanyl did not produce pruritis in any of our patient. Higher sedation scores in midazolam group can be explained by the cephalad spread of midazolam in CSF or its systemic absorption. The haemodynamics was stable and comparable in both the groups. 3 patients in group F required IV nitroglycerine to control high SBP. The autonomic blockade was limited with low dose ropivacaine. To the best of our knowledge, ours is the first study to combine midazolam to low dose plain ropivacaine for elderly patients undergoing TURP under spinal anaesthesia.

Conclusions

Spinal anaesthesia with isobaric ropivacaine provides an adequate sensory and motor blockade with stable haemodynamics for elderly men with age related comorbid diseases undergoing endoscopic urological procedure.There is an equivocal evidence for fentanyl and midazolam as safe and effective adjuvants to ropivacaine anaesthesia.

Author's Contributions and Authorship

MA- Study design, Patient recruitment, Data collection,drafting the article..

AS- Conception and design of study, Drafting and revising the article critically for intellectual content, Final approval of the manuscript

NP- Study design, Patient recruitment, Final approval of the manuscript.

PD- Statistical analysis and interpretation, Revising the final draft and approving before submission

MS- Statistical analysis and interpretation, Revising the final draft and approving before submission

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