

Comparison of Intrathecal Fentanyl and Buprenorphine in Urological Surgery

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Abstract

Objective: To evaluate and compare the characteristics of spinal block, its postoperative analgesic effects and side effects using intrathecal bupivacaine and its combination with fentanyl or buprenorphine in elderly patients undergoing urological surgery.

Methods: Sixty patients aged sixty and above scheduled for elective transurethral resection of prostate (TURP) randomly received hyperbaric bupivacaine 0.75% 2 ml (group L control, n = 20), buprenorphine 30g with hyperbaric bupivacaine 0.75% 2 ml (group B, n = 20) or fentanyl 10g with hyperbaric bupivacaine 0.75% 2 ml (group F, n = 20). Characteristics of spinal block, haemodynamic stability, postoperative analgesia and incidence of adverse effects were compared. All patients were followed for twenty four hours.

Results: The patients' blood pressures remained within 20% of baseline values. The mean time for the sensory block to reach T10 dermatomal level was 3.2 ± 2 minutes in fentanyl-bupivacaine group versus 4.3 ± 1 in buprenorphine-bupivacaine and 4.5 ± 2 bupivacaine alone group. The duration of sensory block was significantly longer in buprenorphine-bupivacaine group. Median block levels reached T8 in all groups. All patients required postoperative analgesia in group L and F except 6 in buprenorphine group.

Conclusion: Buprenorphine 30g in combination with bupivacaine 0.75% 2 ml provided analgesia of comparable clinical onset and longer duration but was associated with a clinically increased incidence of nausea and vomiting in elderly patients (JPMA 56:277;2006).

Introduction

Transurethral resection of the prostate (TURP) is one of the most common procedures performed in elderly men with spinal anaesthesia as the technique of choice.¹ Spinal anaesthesia is the fastest, most predictable and reliable form of regional anaesthesia. By adding a small dose of narcotics to local anaesthetic solution the duration of anaesthesia and analgesia can be significantly prolonged.²

Intrathecal narcotics enhance the sensory blockade of local anaesthetics without affecting the sympathetic activity.³ Intrathecal morphine provides prolonged postoperative analgesia but is associated with increased risk of nausea, vomiting, itching and respiratory depression.⁴ The risk of respiratory depression may be further enhanced in the elderly.⁵ Short acting narcotics like fentanyl and sufentanil have been used intrathecally in elderly population undergoing total hip replacement and provided adequate pain relief of short duration.⁶ Buprenorphine a mu receptor agonist with low intrinsic activity can also be administered safely in the subarachnoid space.⁷ It has a high molecular weight and lipophilicity which may prevent its rostral spread. When used intrathecally in combination with bupivacaine it has improved the quality and duration of postoperative analgesia compared to bupivacaine alone.⁸

There is paucity of literature comparing intrathecal buprenorphine and its quality of analgesia to other narcotics used by intrathecal route. In current literature this use has

not been addressed in any prospective, double blind, randomized trial. On this basis we designed a double blind controlled study to evaluate and compare the characteristics of spinal block and its side effects in elderly patients undergoing transurethral resection of prostate (TURP) who received a subarachnoid block with bupivacaine alone, or with the addition of buprenorphine or fentanyl.

Patients and Methods

The study was approved by the Human Subjects Protection Committee of the Hospital and informed consent was obtained from all subjects. We designed a randomized, double blind controlled trial to evaluate and compare the spinal block characteristics in three different groups. Main end points looked at were onset of sensory block, additional intraoperative analgesic requirements, duration of analgesia and haemodynamic changes. Ancillary end points were twenty four hours analgesic requirements and adverse effects.

Sixty male, American Society Anesthesiologists (ASA) grade I, II or III patients, aged 60 or above scheduled for transurethral resection of prostate were selected. Patients who required general anaesthesia or with bleeding diathesis or history of allergy to narcotics were excluded. The included subjects were randomly assigned to three groups by the sealed-envelope technique. Grouping was based on spinal injectate and was as follows: Group L

(Local anaesthesia alone) received 15 mg 2 ml of 0.75% hyperbaric bupivacaine alone (Abbott Laboratories Pakistan Limited, Karachi), group F received 10 µg of fentanyl mixed with 2 ml of 0.75% hyperbaric bupivacaine and group B received 30 µg of buprenorphine mixed with 2 ml of 0.75% hyperbaric bupivacaine.

Both fentanyl and buprenorphine were measured in insulin syringes (1 ml) for accuracy before being added to bupivacaine. The injectate volume (0.1 ml) in group F and B did not make a significant difference to the total volume injected. The injectate syringes were prepared by one researcher and administered by an anaesthetist unconnected with the study, to maintain blindness of the study.

All patients were premedicated with midazolam 7.5 mg orally approximately one hour before scheduled arrival in the operating room. Before spinal blocks, each patient was preloaded with 7 ml kg⁻¹ of Lactate Ringer solution. Monitoring included continuous electrocardiogram, pulse oximetry and noninvasive blood pressure. Positioning, equipment and technique for lumbar puncture were standardized and all lumbar punctures were performed in the sitting position using a 25 gauge pencil point needle (B Braun) in the midline position at L3-4 interspace. Injections were made over 10-15 seconds. Immediately after injection the patient was turned to the supine position and given 2 litres min⁻¹ of oxygen with McCormick mask. No further sedation was used. Pinprick testing was used every minute to check the onset and to establish the peak level of block. Each side was tested separately with a short beveled needle. Dermatome testing was performed by an anaesthesiologist blinded to patient grouping.

The time of onset of motor block was first noted when the patient said that his legs were getting heavy and subsequently at 5, 10 and 15 minutes after the subarachnoid injection. Motor block was assessed by using the Bromage scale, i.e., no paralysis 0; inability to raise extended leg against gravity but able to flex knee 1; inability to flex knee but able to flex ankle 2; unable to flex ankles but able to wriggle toes 3. The motor block assessment was done on both sides every five minutes for fifteen minutes. Inadequate anaesthesia was to be treated with intravenous narcotics and conversion to general anaesthesia if the supplementation was inadequate.

If the blood pressure fell to less than 90 mm systolic it was to be treated with intravenous ephedrine boluses of 10 mg to a maximum of 30 mg. Bradycardia was to be treated with atropine iv 0.02 mgkg⁻¹ if heart rate fell to less than 60 beats min⁻¹.

The time for the sensory block to reach T10 level was noted. Time of surgical cleaning and start of cystoscopy

and time of end of surgery were also noted. The noninvasive blood pressure (NIBP), pulse rate, oxygen saturation and respiratory rate were charted every five minutes throughout surgery.

The time of arrival in recovery room was noted. Both sensory and motor block were assessed every ten minutes in the recovery room for sixty minutes. Any fall in respiratory rate of less than ten per minute or nausea/vomiting, drowsiness or pruritis was noted. Any complaint of pain by the patient was treated with a rescue analgesic of 10 mg of Pethidine intravenously. Patients were discharged to the ward according to the departmental guidelines and only after the sensory and motor blocks started regressing.

In the ward, patients were assessed at four, eight and twenty-four hours following surgery. All recovery room and postoperative assessments were done by blinded residents. Time of first analgesic given, total analgesic requirements within twenty four hours and the time and dose of analgesic drug given were also noted in addition to monitoring drowsiness, pruritis and respiratory rate.

Computerized statistical analysis was performed using SPSS 11.0.⁹ Data were presented as mean $\pm$ SD. Haemodynamic data including heart rate, systolic and diastolic blood pressure were compared by repeated measure ANOVA. Motor characteristic and sensory level were also tested with ANOVA. P value of < 0.05 was considered significant.

Results

There were twenty patients in each study group. The groups were comparable with regards to age, weight, height, duration of surgery and baseline haemodynamic data (Table 1). No patient was excluded from the analysis because of protocol violation.

Haemodynamic variables

Following subarachnoid injection there was a significant fall in systolic and diastolic pressures in all three groups compared to the baseline, but none of the patients fulfilled the criteria for receiving ephedrine. No significant difference was observed in systolic and diastolic blood pressures measurements between groups at baseline, after spinal injection, onset of spinal anaesthesia, 5, 10, 15 and 20 minutes after onset of anaesthesia and at start of cystoscopy and surgery.

A significant difference in heart rate response was seen in groups F and B patients, where the heart rate was significantly lower compared to group L at fifteen minutes after the subarachnoid injection.

Haemodynamic measurements in the recovery room

Table 1. Demographic and baseline data Mean (SD).

	Groups			p-value
	L (SD) (n=20)	F (SD) (n=20)	B (SD) (n=20)	
Age (yr)	63.3 (8)	58.6 (21)	67.5 (8)	0.157
Weight (kg)	64.7 (12)	67.0 (10)	63.0 (10)	0.532
Height (cm)	171.6 (10)	163.3 (17)	163.3 (17)	0.139
Duration of surgery (min)	75.7 (10)	75.2 (20)	70.1 (14)	0.053
Baseline systolic blood pressure (mm Hg)	134.1 (17)	144.7 (17)	134.4 (23)	0.223
Baseline diastolic blood pressure (mm Hg)	78.5 (10)	85.1 (9)	80.2 (14)	0.250
Baseline heart rate (beats.min ⁻¹)	74.6 (15)	77.7 (17)	79 (13)	0.727
Baseline respiratory rate (rate.min ⁻¹)	14 (2)	15 (3)	15 (4)	0.768

L: Local anaesthetic (Bupivacaine) alone group

F: Bupivacaine and fentanyl group

B: Bupivacaine and buprenorphine group

Table 2. Sensory block characteristics Mean (SD).

	Groups			p-value
	L (SD)	F (SD)	B (SD)	
Onset of sensory block (min)	3.3 (1)	3.2 (2)	3.15 (1)	0.94
Mean time for block to reach T ₁₀ level (min)	4.5 (2)	3.2 (2)*	4.3 (1)	0.04
Mean time to achieve maximal level (min)	15 (2)	10 (3)	15 (3)	0.01
No. of patients showing regression to L1 level at one hour postoperatively	15 (57%)	14 (70%)	7* (35%)	0.001

L: Local anaesthetic (Bupivacaine) alone group

F: Bupivacaine and fentanyl group

B: Bupivacaine and buprenorphine group

* Statistically significant difference from groups L and F

Table 3. Motor block characteristics Mean (SD).

	Groups			Significance p-value
	L (SD)	F (SD)	B(SD)	
Onset of motor block (min)	4.35 (2)	4.95 (1)	5.1 (1)	0.21
Time to achieve maximum block (min)	13.9 (5)*	10.5 (2)	12.2 (3)	0.01
No. of patients with Bromage scale 0 at four hours postoperatively	20	20	20	0.001

L: Local anaesthetic (Bupivacaine) alone group

F: Bupivacaine and fentanyl group

B: Bupivacaine and buprenorphine group

* Statistically significant difference from groups F and B

did not show any significant difference between groups.

Sensory blockade (Table 2)

No significant difference was seen among the three groups on comparing the onset time of sensory block. The mean time for the block to reach the T₁₀ dermatomal level was significantly lower in the fentanyl group 3.2 ± 2 minutes compared to 4.3 ± 1 minutes in buprenorphine and 4.5

± 2 minutes in the bupivacaine only groups (p 0.04). Time to achieve the maximum level of block was also earlier in the fentanyl group (p < 0.001).

The upper level of analgesia in individual patients after subarachnoid administration of drug was above T₁₀ in 19 patients in group L and in all patients in group F and B. The median height of block achieved assessed by needle prick was similar in all groups. Only thirty five percent of the patients in the buprenorphine group showed a regression

of sensory level to L₁ sixty minutes postoperatively compared to seventy and seventy five percent in group L and F respectively ($p < 0.001$). None of the patients required systemic rescue analgesia intra-operatively.

Motor blockade (Table 3)

On comparing the onset of motor block, maximum level achieved and state of motor block at four hours postoperatively, no significant difference was seen among groups. However, less time was required in group F to achieve maximum blockade i.e. 10.5 ± 2 minutes compared to 13.9 ± 5 and 12.2 ± 3 minutes in groups L and B ($p < 0.014$).

Complications

No apparent complications were observed in our patients except PONV which was highest in group C. One patient in group L, three in group F and five in group B complained of nausea or vomiting in the recovery room but this did not reach statistical significance. Vasopressor was not required intra or in immediate postoperative period in any patient. Atropine was not needed for treatment of bradycardia. No episode of desaturation (SaO₂ falling below 92%) was seen. None of the patients complained of pruritis. None of the patients had a respiratory rate less than 10 minutes at any time during observation period. In no patient additional narcotic supplementation was needed to augment analgesia intraoperatively.

Postoperative Analgesia

The mean time from spinal injection to the first requirement of postoperative analgesia was 463 ± 28 minutes in group L, 534 ± 35 minutes in group F and 834 ± 59 minutes in group B ($P < 0.01$). All patients required postoperative analgesia in the first twenty four hours except six patients in group B who did not require any analgesic drug during the study period.

Discussion

Spinal anaesthesia is a commonly used technique for TURP requiring a block from T₁₀ to S₄. The operation is almost always performed in an elderly population with co-existing medical problems. Spinal anaesthesia is the method of choice requiring little anaesthetic drug with minimal physiological disturbance and allows early recognition of complications of prostrate surgery.¹⁰ Incidence of post lumbar puncture headache is also less in this elderly patient population.¹¹

Drugs with longer duration of action may have advantages in these patients such as comfortable painfree recovery with decreased requirement of systemic analgesics. Local anaesthetics alone were administered for

spinal anaesthesia for several years but combination of narcotics and local anaesthetics administered intrathecally have a potent synergistic effect.¹² The addition of narcotics also allows a decrease in the amount of local anaesthetic administered. Laboratory studies have also indicated that all local anaesthetics are neurotoxic in high concentration and spinally administered narcotics seem to have a low potential of neurotoxicity.¹³

The effect of lipophilic narcotics like fentanyl is brief because of its rapid clearance from spinal cord sites.¹⁴ Buprenorphine is a lipid soluble drug and rapid absorption into the spinal venous plexus allows minimal increase in spinal fluid concentration with minimal risk of respiratory depression associated with rostral spread.⁸ It has a high affinity for narcotics receptors and therefore produces longer duration of analgesia compared to other agents.¹⁵ All these characteristics were confirmed in our study

Spinal anaesthesia with bupivacaine and fentanyl has been used in geriatric patients (70-83 years) undergoing knee or hip replacement surgery resulting in decreased postoperative pain intensity and preservation of cognitive function.¹⁶ Intrathecal buprenorphine in a dose of 30 or 45 µg has also been used in combination with bupivacaine in elderly patients undergoing TURP and orthopaedic procedures showing it to be an effective analgesic suitable for management of postoperative pain in elderly patients.^{8,17} Fentanyl 10gs and Buprenorphine 30gs were chosen because they were considered equipotent to one mg of morphine.

A fall in both systolic and diastolic pressure of similar magnitude was observed in all three groups following the subarachnoid blockade. This is due to the decrease in sympathetic efferent activity after spinal anaesthesia and is said to be dose related to bupivacaine. Fentanyl has been shown not to cause further depression of sympathetic activity in animal experiments when added to bupivacaine in dogs. Subjects in our study although showed a similar fall in blood pressure but a significant difference in the heart rate response was observed where heart rate was observed to be significantly lower in both groups where intrathecal narcotic was added. This could reflect an additional effect of neuraxial narcotics on further reduction of sympathetic flow. This needs to be studied further.

Elderly patients are said to be more susceptible to respiratory depression due to narcotics.⁵ The reason stated is that narcotics cumulation changes as a result of progressive decrease in clearance with aging. No fall in respiratory rate or desaturation less than 92% was seen in the recovery room in our patients. Stoelting has recommended that patients receiving intrathecal narcotics should be under close surveillance for adequacy of

breathing but suggests that low dose neuraxial administration of narcotics does not obligate observation in an intensive care environment.⁵

Hyperbaric solution was used by us because of its safety and reliability. With hyperbaric solutions posture has no influence.¹⁸ Hyperbaric solutions are also associated with lesser incidence of respiratory depression.⁸

Postoperative nausea and vomiting is also common with the use of intrathecal narcotics. In a previous study on intrathecal buprenorphine in orthopaedic surgery three out of thirty patients (10%) in the bupivacaine group had postoperative nausea and vomiting (PONV) compared to ten out of thirty (33%) with 300 µg buprenorphine with 1 ml of 1% hyperbaric bupivacaine.¹⁷ Capogna, et al also observed PONV in eleven patients out of thirty (34%) receiving 30 µg buprenorphine in combination with hyperbaric bupivacaine and in fourteen patients who received a dose of 45 µg of buprenorphine.⁸ The incidence of PONV in our patient population was 25% in the buprenorphine and 15% with fentanyl. This was slightly less than the incidence in other studies. This PONV though not statistically significant because of the small number of patients (Type 2 error) is of clinical significance. We did not measure the severity of nausea or vomiting in our patients.

Studies involving intrathecal fentanyl and bupivacaine in elderly patients did not show a significant rise in the incidence of PONV when 25µg of fentanyl was added to 12.5µg of hyperbaric bupivacaine solution in comparison to bupivacaine alone.¹⁶ The only side effect with statistically increased incidence was pruritis where it was observed in 21% patients compared to none in the control group. None of our patients complained of pruritis in the above study. No difference was observed in the onset, offset or characteristics of the block.

A much higher dose of 300µg of buprenorphine was used intrathecally by Sen¹⁷ in combination with one ml of hyperbaric bupivacaine in elderly patients undergoing lower limb orthopaedic surgery. No significant side effect was observed except PONV in 33%.

Our study has demonstrated that the use of bupivacaine with fentanyl (10g) spinal anaesthesia resulted in the earlier onset of both sensory and motor block compared to buprenorphine and bupivacaine combination but the duration was longer with the latter combination. This earlier onset though statistically significant may not be of high clinical significance. Both techniques were associated with haemodynamic stability and no vasopressor support was required. In conclusion the use of buprenorphine 30g in combination with bupivacaine 0.75% 2 mls provided postoperative analgesia in elderly patients undergoing urological procedures but with a clinically increased incidence of

nausea and vomiting. It can be used in countries where fentanyl may not be available.

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