Original Article

Effects of intrathecal dexmedetomidine as an additive to low-dose bupivacaine in patients undergoing transurethral resection of prostate

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ABSTRACT

Background and Aims: In patients undergoing transurethral resection of prostate (TURP), it is vital to restrict the level of block to T_{10} dermatome during spinal anaesthesia. Low-dose bupivacaine causes minimum haemodynamic alterations, but may provide insufficient surgical anaesthesia. Dexmedetomidine, a selective α_2-adrenoreceptor agonist, is a potent anti-nociceptive agent when given intrathecally. The aim of this study was to compare the adjuvant effects of intrathecal dexmedetomidine with low-dose bupivacaine spinal anaesthesia versus a higher dose of bupivacaine in patients undergoing TURP. **Methods:** The study was designed as a prospective, double-blind, randomised trial that included sixty patients of American Society of Anesthesiologists Grade I–III scheduled for TURP. They were allocated into two groups: Group I receiving only hyperbaric bupivacaine intrathecally and Group II receiving dexmedetomidine with low dose bupivacaine. The time to regression of two dermatomes from the peak sensory block level was the primary outcome of the study. **Results:** With comparable baseline and demographic attributes, both groups had similar peak sensory block levels (T_9). Patients in Group II had quicker onset with the time to reach T_{10} being faster (10.72 ± 3.50 vs. 12.72 ± 3.90 min, $P = 0.041$), longer duration of motor block (200 ± 18.23 vs. 190 ± 10.15 min, $P = 0.011$) and increased time to first analgesic requirement (300 ± 25.30 vs. 220 ± 15.12 min, $P = 0.0001$). **Conclusion:** Intrathecal dexmedetomidine with low-dose bupivacaine provides faster onset, prolonged sensory and motor block and reduced rescue analgesic requirement in patients undergoing TURP.

Key words: Additives, dexmedetomidine, spinal anaesthesia

INTRODUCTION

Spinal anaesthesia is the most routinely used procedure for transurethral resection of prostate (TURP). Sensory block up to T_{10} is considered favourable to abolish the discomfort caused by bladder distension. Sensory block cephalad to this hides the capsular signs associated with bladder perforation and may hamper its early diagnosis and treatment. Moreover, because of the restricted cardiovascular and respiratory reserves in older patients undergoing TURP, it is important to limit the cephalad spread to lessen haemodynamic changes.[1] Smaller doses of local anaesthetic in combination with additives provide the required sensory level with appropriate analgesia.[2]

Dexmedetomidine is the S-enantiomer of medetomidine with a high degree of specificity for α2-adrenoreceptor (α_2:α_1, 1620:1).[3] To date, limited studies have been reported on the influence of intrathecal dexmedetomidine on spinal block with bupivacaine for urological procedures.[4]

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The aim of this study was to compare the characteristics of spinal block, haemodynamic changes and total analgesia requirements, following administration of intrathecal 3 μg dexmedetomidine combined with a low dose (6 mg) of bupivacaine versus a higher dose of 7.5 mg 0.5% hyperbaric bupivacaine in elderly patients undergoing TURP.

METHODS

The study was initiated after approval by the Institutional Ethical Committee. It was a prospective randomised, double-blind study conducted between October 2015 and April 2016 and informed consent was acquired from all the participants. Patients with a history of spine surgery or the presence of an infectious focus on the back, hypersensitivity to local anaesthetics or dexmedetomidine, coagulopathy, cooperation difficulty, neurological disorders or severe hepatic failure were excluded from the study.

Sixty elderly male patients in the age group between 55 and 75 years and American Society of Anesthesiologists (ASA) Grade I–III undergoing TURP were included in this study. Using a computer-generated random number table, patients were enrolled in one of the two groups: Group I receiving 7.5 mg of 0.5% hyperbaric bupivacaine hydrochloride and Group II receiving 3 μg of dexmedetomidine hydrochloride combined with 6 mg of 0.5% hyperbaric bupivacaine hydrochloride. Each patient received an appropriate randomised number allocated to his/her group according to the number, sealed and packed inside opaque covers and labelled with the project title, investigators' name and the randomisation number. No anaesthesiologist or assessor taking part in the present study was aware of the group assignment until the entire sixty patients were included and the assessment was completed.

All patients were instructed not to consume solid food after midnight prior to surgery and to take clear liquids upto 2 hours before surgery. Thirty minutes prior to surgery tablet metoclopramide 10 mg and tablet ranitidine 150 mg orally was given to the patients.

On arrival at the Operating Room (OR) monitors like non-invasive blood pressure monitor (NIBP), peripheral oxygen saturation monitor (SpO2), electrocardiography monitor (ECG) having lead II and lead V4 were attached. All the baseline values of blood pressure (SBP, DBP and MAP), heart rate and SPO_2 were observed and recorded. Intravenous access was obtained with 18G IV cannula in a dorsal vein of non-dominant hand and free flow of intravenous fluid checked.

Patients were pre-loaded with 300 mL of 0.9% sodium chloride solution prior to anaesthesia.

The study drug solutions looked identical and were prepared by an investigator who was not involved in monitoring or study analysis. Dexmedetomidine 100 μg/mL was diluted with normal saline to 10 μg/mL in a 10 mL syringe. From this diluted mixture, 0.3 mL of dexmedetomidine was drawn with the help of a 1 mL BD syringe and added to the 6 mg of hyperbaric bupivacaine in Group II under complete aseptic conditions. The total volume of drug solutions was 1.5 mL in each group. A senior OR staff supervised and ensured the sterility of the prepared drugs and left the OR along with the investigator preparing the study drugs immediately after the preparation of study medication to ensure optimum blinding. The principal investigator had done all the monitoring including intra- and post-operative anaesthetic variations and complications and was unaware of the drug used in different groups.

Spinal puncture was performed at L_3–L_4 or L_4–L_5 with a midline approach using a 25-gauge Quincke needle in the sitting position. After verification of clear and free flow of cerebrospinal fluid, the drug was administered and the patients were placed in the supine position. The anaesthesiologist recording the data, patients, surgeon and the nursing staff were blinded to assignment of the patient group.

The primary outcome of this study was the comparison of two sensory dermatomes' regression time from peak sensory block level. The other objectives were assessment of the motor block scales, haemodynamic alterations as well as the intra- and post-operative analgesic requirements in both the groups.

The sensory block levels were checked on the bilateral midthoracic line with pinprick using a blunt needle every 2 min from the drug injection. The surgeon was asked to start the surgery when the sensory block had reached to T_{10} level or stabilised for four consecutive tests, whichever occurred earlier. Sensory level was then assessed every 10 min until two-segment regression. The degree of motor block was monitored using the modified Bromage scale (0 = no motor block; 1 = hip blocked; 2 = hip and knee blocked;

and 3 = hip, knee and foot blocked), assessed at the end of surgery and every 15 min postoperatively until complete motor recovery (Bromage scale 0).

For each of the patients, heart rate (HR) and mean arterial pressure (MAP) were monitored every 2 min for the first 10 min after spinal anaesthesia, then every 5 min until 30 min and then every 30 min until motor and sensory recovery. Patients were said to have developed bradycardia if the HR went below 40 while hypotension was defined as a MAP of <50 in our study. If a patient complained of discomfort or pain intraoperatively, injection fentanyl (100 μg) was administered intravenously. In the occurrence of an inadequate spinal block (defined as pain terrible enough to hamper the surgical procedure), general anaesthesia was promptly induced and the cases were considered as failure.

Post-operative pain assessment was done using an 11-point visual analogue scale (VAS), with 0 indicating no pain and 10 indicating the worst possible pain. In the post-anaesthesia care unit, pain was treated with injection of tramadol (50 mg) given intravenously as rescue analgesic, whenever the patients demanded and/or pain score reached 3. Pain was assessed hourly for the first 8 h after operation, and every 4 h thereafter for a total of 24 h.

Injection ondansetron (4 mg) intravenously as needed was prescribed for nausea and vomiting.

Adverse events (bradycardia, hypotension, nausea, shivering, vomiting and pruritus) were documented during surgery and recovery. Numeric Sedation Scores (1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus and 5 = asleep and not responsive to any stimuli) were used to record the intra-operative sedation levels. The sedation score was assessed every 15 min for 1 h intraoperatively.

The time to first analgesic dose, amount of tramadol administered after operation and the occurrence of any post- or intra-operative complications, including vomiting, nausea, itching, respiratory depression and postdural puncture headache, were recorded and accordingly treated.

The primary outcome of our study was the time to the regression of two dermatomes from the peak sensory block level, which was based on a previous well-established study.[5] The mean time ± SD to the sensory regression of two dermatomes was 122 ± 37 min and 80 ± 28 min in the dexmedetomidine group and plain group, respectively, in the previous study. Sample size was calculated using an $\alpha = 0.05$ and a power of 80%, which came up to be 24 patients required per group to detect a 25% difference in time for 2-segment dermatome sensory regression. We included thirty patients per group to allow for possible dropout.

The Student's *t*-test was used to analyse age, weight, height, duration of surgery, baseline and lowest blood pressure, recovery times of sensory and motor block, VAS score, total duration of analgesia and total requirement of rescue analgesia. Intergroup differences of the amount of intra-operative analgesic used, peak sensory block level and maximum motor block score were tested with the Mann–Whitney *U*-test. Test of proportion (*Z*-test) was used to test the significant difference between two proportions. Values were expressed as mean ± SD. Statistical analysis was done by the Statistical Package for the Social Sciences (SPSS) 15 (SPSS Inc., Chicago, Illinois, USA), and $P < 0.05$ was considered statistically significant.

RESULTS

No patient had to be excluded or considered a failure in the study. The baseline demographic characteristics (age, weight and ASA grade) of the two groups of patients were comparable [Table 1].

Cardiovascular parameters (HR and MAP) were similar in both groups [Figure 1].

The mean time taken to reach T_{10} sensory block was significantly lower in Group II (10.72 ± 3.50 min) compared with Group I (12.72 ± 3.90 min) ($P = 0.041$). Peak sensory block levels were similar in both the groups ($P = 0.418$) while the median peak

Table 1: Comparison of demographic and baseline characteristics

Characteristics	Group I (*n*=30)	Group II (*n*=30)	*P*
Age (years)	66.1±5.8	64.9±4.1	0.359
Weight (kg)	65.0±9.1	64.3±9.5	0.772
Duration of surgery (min)	82.6±15.8	83.9±15.5	0.749
ASA physical status			
I	9 (30)	11 (36.7)	1.000
II	20 (66.7)	17 (56.7)	
III	1 (3.3)	2 (6.6)	

Data represented as mean±SD or number of patients, *n* (%). ASA – American Society of Anesthesiologists; SD – Standard deviation

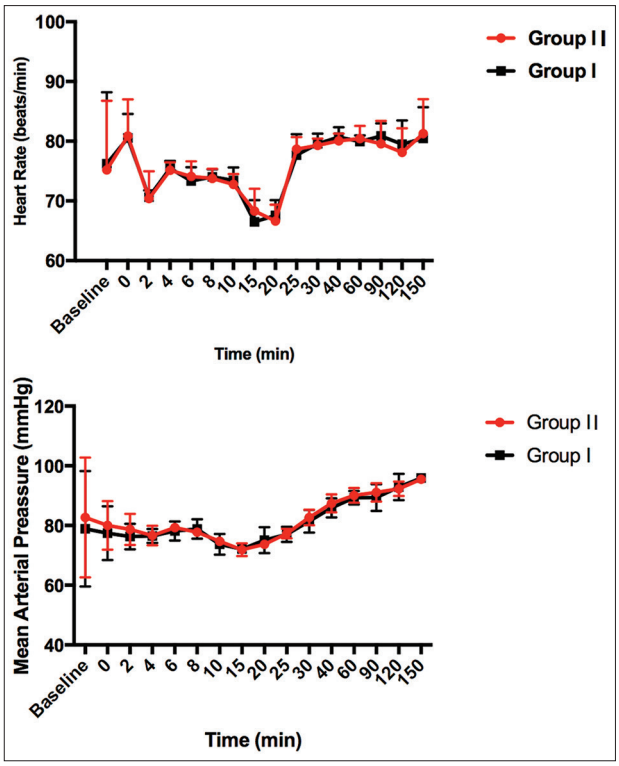

Figure 1: Cardiovascular parameters (mean arterial pressure and heart rate)

level of sensory block was T9 in both groups. Duration of two-segment sensory regression was 130.80 ± 15.20 min in Group II compared with 116.40 ± 20.12 min in Group I ($P = 0.003$).

Motor block lasted for a longer duration in Group II than in Group I and it was statistically significant ($P = 0.011$) [Table 2].

None of the study patients developed bradycardia (HR <40) or severe hypotension (MAP <50). All patients showed a sedation score <2 at every time point intraoperatively. Group II patients had better intra- and post-operative analgesia, low VAS scores and reduced analgesic requirements [Tables 3 and 4]. Seven patients required injection fentanyl 100 μg in Group I intraoperatively, thus the total intraoperative rescue analgesic requirement was 0.7 mg in the group [Table 2].

There were no significant differences between groups regarding post-operative adverse effects [Table 5].

DISCUSSION

An important endpoint of this study was to determine time to regression of two sensory dermatomes from the peak sensory block level. In our study, 3 μg of

Table 2: Comparison of block characteristics

Characteristics	Group I (*n*=30)	Group II (*n*=30)	*P*
Time to reach T_{10} sensory block (min)	12.7±3.9	10.7±3.5	0.041
Peak sensory block level			
T_7	0	0	0.418
T_8	2 (6.7)	1 (3.3)	
T_9	13 (43.3)	15 (50)	
T_{10}	10 (33.3)	14 (46.7)	
$>T_{10}$	5 (16.7)	0	
Median peak sensory level	T_9	T_9	
Modified Bromage score at the end of surgery			
0	0	0	0.896
1	3 (10)	0	
2	12 (40)	16 (53.3)	
3	15 (50)	14 (46.7)	
Time to two-segment regression (min)	116±20.1	130±15.2	0.003
Time to motor recovery (min)	190±10.1	200±18.2	0.011
Patients requiring intraoperative rescue analgesic fentanyl (%)	7 (23.33)	0	0.0048
Time to first post-operative analgesic requirement (min)	220±15.1	300±25.3	0.0001

Data represented as mean±SD or number of patients, *n* (%). SD – Standard deviation

Table 3: Comparison of visual analogue scale scores

VAS score	Group I (*n*=30)	Group II (*n*=30)	*P*
1 h post-surgery	2.20±0.77	1.64±0.60	0.003
2 h post-surgery	3.10±1.78	2.00±1.69	0.017
3 h post-surgery	2.10±0.90	1.99±1.50	0.732
4 h post-surgery	1.99±1.10	1.22±0.67	0.0002

Data represented as mean±SD. SD – Standard deviation; VAS – Visual analogue scale

Table 4: Comparison of rescue analgesia consumption in the two groups

Characteristics	Group I (*n*=30)	Group II (*n*=30)	*P*
Number of rescue analgesics given within 24 h			
3	2 (6.67%)	7 (23.33%)	0.073
4	17 (56.67%)	19 (63.33%)	0.601
5	7 (23.33%)	4 (13.33%)	0.320
6	4 (13.33%)	0 (0%)	0.040
24-h analgesic (tramadol) consumption (mg)	332.50±61.29	292.50±45.56	0.006

Data represented as mean±SD or number of patients. SD – Standard deviation

Table 5: Intraoperative side effects

Side effects	Group I (*n*=30)	Group II (*n*=30)	*P*
Nausea	2 (6.67%)	2 (6.67%)	1.000
Hypotension	2 (6.67%)	3 (10%)	0.643
Bradycardia	3 (10%)	3 (10%)	1.000
Vomiting	1 (3.33%)	2 (6.67%)	0.556
Respiratory depression	0	0	
Pruritus	0	0	
Shivering	2 (6.67%)	2 (6.67%)	1.00

intrathecal dexmedetomidine prolonged the duration of sensory block compared to the control group. The time to reach peak block level was shorter as well in the dexmedetomidine group than in the control group. Furthermore, time to motor recovery (duration of motor block) was longer with dexmedetomidine than in the plain bupivacaine group. In the dexmedetomidine group, post-operative analgesic demand was less and the time to first analgesic request was longer compared to the control group.

Patients undergoing TURP are generally elderly with various comorbidities.[6] Thus, it is crucial to limit the block level to minimise the haemodynamic instability during spinal anaesthesia. Although there are a number of factors influencing the spinal block level, block level could be more influenced by total dosage of drug and not by the drug volume, concentration or block position.[7-9] Therefore, the dose of intrathecal local anaesthetic should be decreased to limit the block level. It is a concern for most anaesthesiologists that a reduced dose of local anaesthetic may provide insufficient spinal block. Thus, there have been many trials to reduce the dose of intrathecal local anaesthetics and improve the block quality with co-administration of additives such as opioids or clonidine.[10,11] However, combined additives can induce their own side effects such as bradycardia, hypotension, vomiting, nausea, pruritus and excessive sedation.[12,13]

Dexmedetomidine is a potent and selective α_2-adrenoreceptor agonist. The antinociceptive properties of intrathecal α_2-adrenoreceptor agonists are manifested by suppressing the release of C-fibre transmitters, hyperpolarisation of post-synaptic dorsal horn neurons and inhibition of release of substance P.[14] In addition, the effectiveness of α_2-adrenoreceptor agonist has been shown to correspond well with their binding affinity to spinal α_2-adrenoreceptors.[15]

To date, there have been limited clinical human studies on intrathecal dexmedetomidine.[16,17] In those studies, it was established that 3–15 μg of dexmedetomidine co-administered with local anaesthetics has a dose-dependent effect on anaesthetic onset and duration with better haemodynamic stability. Although an ideal dose of intrathecal dexmedetomidine has not been established, 3 μg of dexmedetomidine seems to be appropriate for potentiating the analgesic efficacy of low-dose spinal anaesthesia as seen from previous studies.[18]

In the current study, 3 μg of dexmedetomidine with 6 mg bupivacaine produced similar peak sensory block levels compared to the control group but a lower mean time to reach the T_{10} block level and a prolonged duration of sensory block. Other studies, that used 10–15 mg as general dose of bupivacaine also, did not show any significant difference in peak sensory block level between bupivacaine group and bupivacaine with dexmedetomidine group, but excessively reached the median block level of T_5–T_6.[19,20]

In our study, the duration of motor block was potentiated by dexmedetomidine in Group II. As seen in animal and human studies, dexmedetomidine prolongs not only the duration of sensory block, but also the degree and duration of the motor block.[21,22] The potentiation mechanism of motor block by dexmedetomidine is not well established, but is suggested to be an additive or synergistic effect to the local anaesthetics, or related to the interference with neuromuscular activity, or binding of α_2-agonists to motor neurons in the dorsal horn.[23]

In this study, the post-operative analgesic requirements were significantly less and the time to the first analgesic request was longer in the group receiving dexmedetomidine than that in the control group [Table 4].

TURP for benign prostatic hyperplasia is frequently performed in elderly patients having cardiovascular limitations with various systemic diseases. We found that more than 65% of patients had more than one systemic disease. Considering this, it is desirable to limit the spinal block level to as low as possible to avoid hypotension owing to high sympathetic block and also to maintain the adequate level of anaesthesia. In our study, both the plain bupivacaine and dexmedetomidine groups had a peak sensory block level of median T_9 and did not produce serious hypotension or bradycardia perioperatively. However, seven patients in the control group who received 7.5 mg of bupivacaine showed a peak sensory block level of $<T_9$, leading to insufficient intraoperative analgesia and discomfort. A small dose of dexmedetomidine intrathecally administered at the lumbar level thus does not seem to cause significant hypotension. Since the sympathetic block is usually near maximal with the usual doses of local anaesthetics, a low dose of local anaesthetics is endorsed to avoid significant hypotension, especially in elderly patients.[24]

In addition, high spinal block is not required for TURP. Taking into consideration the sensory innervations to the prostate, a sensory block up to T_{11} is sufficient for TURP. The prostate and bladder are innervated by both the sympathetic (pelvic plexus, hypogastric plexus) and parasympathetic (S_3, S_4) autonomic divisions. The urethral sphincter should be adequately relaxed for the endoscope to pass freely, and the urethral sphincter is also supplied by the sympathetic division of the pelvic plexus (internal sphincter) and somatic fibres of the pudendal nerve (external sphincter). Studies done earlier suggested that mid-lumbar sensory block is enough for TURP, but sensory block at T_{12}–L_1 at least is recommended to avoid discomfort due to irrigation induced bladder distension.[25] In our study, seven patients in the control group, who showed a peak sensory block level $<T_9$, required fentanyl supplementation for abdominal discomfort during the operation.

Intrathecal α_2-agonists induce a dose-dependent sedative effect in humans.[26] The dose of dexmedetomidine used in our study was at the end of the dosing spectrum. The sedation score was low (<2) in all patients, as in other studies, demonstrating that 3 μg of intrathecal dexmedetomidine may not produce the sedative effects.

Our study is not free of limitations. We could not perform a follow-up for our patients to assess any signs of neurotoxicity or neurologic deficits due to the use of dexmedetomidine in the study group.

CONCLUSION

In conclusion, our study showed that 3 μg of dexmedetomidine added to 6 mg bupivacaine produced a faster onset and longer duration of sensory and motor block as well as prolonged perioperative analgesia without significant haemodynamic alterations, as compared to bupivacaine alone, in patients undergoing TURP.

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Conflicts of interest
There are no conflicts of interest.

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