International Journal of Medical Science and Clinical Research
Online-ISSN: 2664-7761; Print ISSN: 2664-7753
Received: 21-05-2020; Accepted: 08-06-2020; Published: 23-06-2020
www.journalofmedical.com
Volume 2; Issue 2; 2020; Page No. 27-31

Adjuvant effects of intrathecal dexmeditomedine with low dose bupivacaine versus a higher dose of bupivacaine in patients undergoing trans urethral resection of prostate surgery

Rakesh Kalappa[1*], Varsha Kothari[2], Anupama Gupta[3]
[1-3] Department of Anesthesiology, Rajasthan University of Health Sciences, SMS Medical College and attached group of Hospitals, Jaipur, Rajasthan, India

Abstract
The patients undergoing TURP surgeries are elderly who have many comorbities involving multiple organs. It is beneficial if the block height is limited to T_{10} sensory level which is sufficient for TURP surgeries. The aim of the study was to compare the adjuvant effects of dexemedetomidine with low dose bupivacaine in patients undergoing TURP surgeries.
Methods: This prospective, double-blinded, randomised study included sixty patients of ASAGrade I–III scheduled for TURP. They were randomised into two group using computer generated random number table. Group A received 7.5 mg of hyperbaric bupivacaine and Group B received dexmedetomidine (3μg) with low dose bupivacaine (6mg). Outcome variables included time of onset of block, duration of sensory and motor block and, requirement of rescue analgesics.
Results: Baseline and demographic data were comparable among the groups. The time to reach T10 was faster (10.98±1.38 min) in group B than group A (12.49±1.21 min), P = <0.001), longer duration of motor block (133.32±6.6 vs. 118.38±6.47min, P< 0.001) and increased time to first analgesic requirement. (302.37±9.94vs.221.57±7.30min,P<0.0001) were observed in group B
Conclusion: Intrathecal dexmedetomidine with low-dose bupivacaine provides faster onset, prolonged sensory and motor block and reduced rescue analgesic requirement in patients undergoing TURP.

Keywords: additives,bupivacaine, dexmedetomidine, spinal anaesthesia,TURP

1. Introduction
Spinal anaesthesia is most commonly used anaesthetic technique for patients undergoing transurethral prostatectomy (TURP) as comlications like bladder perforation, water intoxication and fluid overload can be recognized early as patient is awake. Most of the patients undergoing TURP are elderly having cardiac, respiratory and other disease, so it becomes necessary to limit the height of spinal block to reduce the impact of adverse cardiopulmonary effects in such patients. Low dose of spinal anaesthetic like bupivacaine can limit the distribution of spinal block and provides comparably rapid recovery but it often provides inadequate level of sensory block.

In the recent years many pharmacological class of drugs are used, which not only provide the better analgesia but also lessens the dose of local anesthetics that were used routinely. A number of adjuvants such as midazolam, opioids, and α_2 agonist have been studied in this regard [1-2]. α_2 agonist, when used as adjuvants to local anaesthetics in regional anaesthesia provides the unique advantage of analgesia and sedation without causing significant respiratory depression[3-4]. Dexmedetomidine is the S-enantiomer of medetomidine with a high degree of specificity for α2-adrenoreceptor (α 2: α 1, 1620:1and 220:1 for clonidine) [5].

This study was designed to evaluate and compare the adjuvant effects of intrathecal dexmedetomidine with low dose bupivacaine versus a higher dose of bupivacaine in patients undergoing TURP under spinal anaesthesia.

2. Methods
The prospective randomised, double-blinded study conducted between April 2018 and March 2019 after approval by Instituitional Ethics Committee and informed written consent from all the patients. Patients with a history of spine surgery, local site infection, hypersensitivity to study drugs, hepatic and neurologic impairment, coagulation disorders, refusal for surgery were excluded from 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. Patients were randomly allocated using computer generated random number table into two groups,A detailed pre anaesthetic checkup was performed day before surgery.

Group A received 7.5 mg of 0.5% hyperbaric bupivacaine hydrochloride and Group B received 3μg of dexmedetomidine hydrochloride combined with 6 mg of 0.5% hyperbaric bupivacaine hydrochloride. Neither the anaesthesiologist nor the patient taking part in the present study were aware of the group allotted.

On the day of surgery, after checking fasting status and consent patient was taken in OT.Intravenous access was established with 20G cannula.Non-invasive blood pressure monitor (NIBP), peripheral oxygen saturation monitor (SpO2), electrocardiography monitor (ECG) were attached. All the baseline values of blood pressure (SBP, DBP and MAP), heart rate and SPO2 were recorded.

Patients were hydrated with 300 mL of 0.9% sodium

chloride solution prior to spinal anaesthesia. The study drug solutions 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 B. The total volume of drug solutions was 1.5 mL in each group.

Under all aseptic conditions,spinal puncture was performed at L3–L4 level with a midline approach using a 25-gauge Quincke needle in the sitting position. After ensuring free flow of CSF, 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 unaware of the study groups.

The sensory block levels were checked bilaterally in the midclavicular line with pinprick test using a hypodermic needle every 2 min from the drug injection till T10 sensory level block was achieved. Sensory level was assessed every 10 min thereafter 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). The primary outcome of this study was the comparison of two sensory dermatomes' regression time from peak sensory block level [6]. The other objectives were onset and duration of the motor block haemodynamic alterations as well as the intra- and post-operative analgesic requirements in both the groups.

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 <65 in our study. If a patient complained of pain intraoperatively, injection fentanyl 100 μg was administered intravenous. If the spinal block was incomplete, general anaesthesia was promptly administered and the cases were excluded from the study. VAS score were used to assess the pain postoperatively and VAS ≥3 was treated with injection of tramadol (50 mg) intravenously as rescue analgesic. Pain was assessed hourly for the first 8 hours after surgery, and every 4 hourly thereafter for a total of 24 hours.

Adverse events (bradycardia, hypotension, nausea, shivering, vomiting, pruritus, respiratory depression and postdural puncture headache) were documented and treated accordingly 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 hour intraoperatively. The time to first analgesic dose, total dose of tramadol administered after operation were noted.

3. Statistical analysis

Sample size was calculated to be 19 patients in each group using an $\alpha = 0.05$ and a power of 80%, to detect a 25% difference in time for 2-segment dermatome sensory regression based on a previous study[6]. Total 30 patients were enrolled in each group for better conclusions.

The continuous variables (quantitative data) like age, weight, height, blood pressure, heart rate, time were presented as mean and standard deviation and analyzed by applying one way –ANOVA test.

The categorical variables (qualitative data) like ASA grade, sedation score were presented in frequency and percentage and were analyzed with Chi-Square test (for nominal data). All the statistical analysis of data was done with statistical programming software–SPSS (Statistical Package for the Social Science) version 20.0.0 (SPSS Inc., Chicago, Illinois, USA). A p value of less than 0.05 was considered statistically significant in all the analysis.

4. Results

The baseline demographic characteristics (age, weight and ASA grade) of the two groups of patients were comparable [Table 1].

The mean time taken to reach T10 sensory block was significantly lower in Group B (10.98±1.38min) compared with Group A (12.49±1.21min) ($P < 0.001$). Peak sensory block levels were similar in both the groups ($P = 0.111$).Duration of two-segment sensory regression was 133.32±6.6min in Group B compared with 118.38±6.47min in Group A (P <0.001).

Motor block lasted for a longer duration in Group B than in Group A and it was statistically significant (P < 0.01) [Table 2]. Incidence of adverse effects was not statistically significant among the groups. All patients showed a sedation score <2 at every time point intraoperatively. Group B patients had better intra- and post-operative analgesia, low VAS scores and reduced analgesic requirements.

Table 1: Demographic variables

Characteristics	Group A (n=30)	Group B (n=30)	P
Age (years)	65.2±9.38	63.23±8.63	0.207
Weight (kg)	62.07±6.36	63.67 ±3.28	0.182
ASA physical status			
I	22	15	0.111
II	8	15	
III	0	0	

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

Table 2: Comparison of block Characteristics

Characteristics	Group A	Group B	P
Time to reach T10 sensory block (min	12.49±1.21	10.98±1.38	<0.001
Median peak sensory block level	T_{10}	T_{10}	0.114
Modified Bromage score at the end of surgery			
0	0	0	0.112
1	4	0	
2	13	15	
3	13	15	
Time to twosegment regression (min)	118.38±6.47	133.32±6.6	<0.001
Time to motor recovery (min)	193.91±4.18	202.20±6.91	<0.001
Time to first postoperative analgesic requirement (min)	221.57±7.30	302.37±9.94	<0.0001

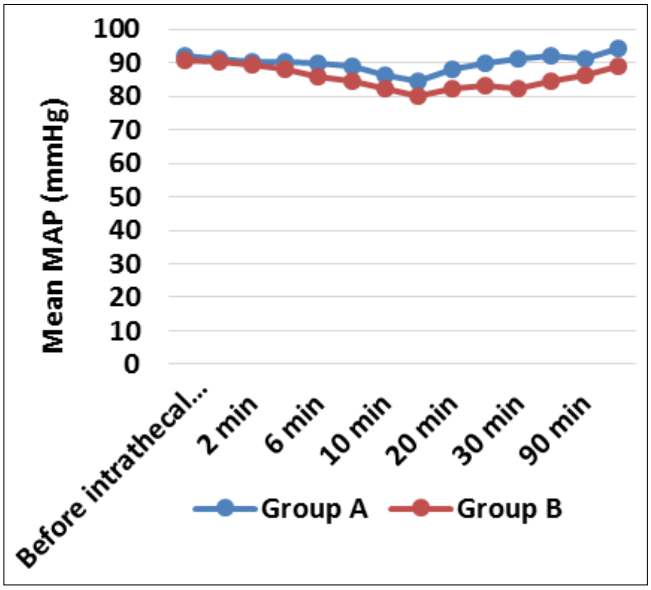

Fig 1

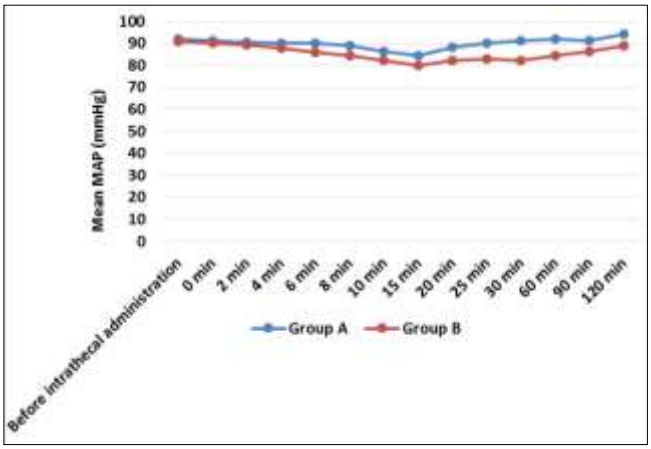

Fig 2

Table 3: Intra operative complications

	Group A	Group B	P value
Bradycardia	1	2	0.757
Hypotension		3	0.212
Respiratorydepression	0	0	
Nausea	2	2	0.346
Vomiting	0	0	
Shivering	1	1	0.215

5. Discussion

Postoperative pain is one of the most distressing complications for the patient. It amplifies the surgery induced stress response, hinders early ambulation and can prolong the time of discharge. Many anaesthetic adjuvant have been used to prolong the duration analgesia into the postoperative period with varying success. These include midazolam, buprenorphine, nalbuphine, fentanyl, α_2 agnoist such as clonidine and dexmedetomidine. α receptors agonists, like clonidine (α_2:α_1::200:1), have been used for pain management for decade. A recent study reported that α_1 receptors activation encountered α_2 related analgesia and showed that an agonist with higher α_2 receptors selectivity would show a more potent analgesic effect and would be more suitable for pain treatment. [7] Dexmedetomidine is a α_2 receptor agonist developed in the 1990's. Various studies indicate that it could prolong the analgesic effects of local anaesthetics, improves the characteristics of regional block, decreases intraoperative anaesthetic requirements and improves postoperative analgesia, regardless of the neuraxial route of administration(eg epidural, caudal, spinal or intravenous). These evidence suggest that dexmedetomidine might be a new drug, promoting the effect of local anaesthesia, and could be used for surgery induced acute pain control [8] It's action on pre synaptic α_2 receptors in the central nervous system decreases the outflow of norepinephrine, leading to anxiolysis, sedation, analgesia and bradycardia.[9] Dexmedetomidine has an inhibitory effect on the locus coeruleus (A6 group) located at the brain stem.

The supraspinal target for these drugs is locus coeruleus, α_2 agonist also act at the level of spinal cord, on the substantia gelatinosa, cause analgesia and vasoconstriction, decreasing the incidence of shivering and delaying the absorption of intrathecally administered, local anaesthetic agent. [10] α 2 agonist also carry the unique advantage of providing analgesia and sedation without causing significant respiratory depression.

In TURP, sensory block up to T10 is 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 [11].

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.[12]

This study was designed to examine and compare the adjuvant effects of intrathecal dexmedetomidine with low-dose bupivacaine versus a higher dose of bupivacaine in patients undergoing TURP under spinal anaesthesia. Onset and regression time of motor and sensory, level of block achieved, duration of analgesia, and incidence of side effects was noted. The mean onset of sensory block was statistically significant different ($P<0.05$) among the group. The onset of sensory block was shorter for Group B compared to Group A. The time for two segment regression was significantly prolonged by dexmedetomidine. Dexemeditomidine significantly prolonged the duration of analgesia, 24 hr analgesic consumption also the duration of motor block was potentiated. 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. [13-14] 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 α2-agonists to motor neurons in the dorsal horn.[15]

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

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 T10 and did not produce serious hypotension or bradycardia perioperatively Intrathecal α2-agonists induce a dose-dependent sedative effect in humans. [16] 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.

5. 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.

6. Financial support

Nil.

7. Conflicts of interest

There are no conflicts of interest.

8. References

1. Hohener D, Bluementhal S, Borgeat A. Sedation and regional anestheisa: in the adult patient. Br J Anaesth. 2008; 100(1):8-16
2. Helgeson LE. Sedation during regional anaesthesia: Inhalation versus intravenous. Curr Opin Anaesthesiol. 2005; 18(5):534-9.
3. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent). 2001; 14(1):13-21
4. Venn RM, Bradshaw CJ, Spencer R. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia.* 1999; 54:1136-42.
5. Jaakola ML, Salonen M, Lehtinen R, Scheinin H. The analgesic action of dexmedetomidine-a novel α2-adrenoceptor agonist-in healthy volunteers. Pain. 1991; 46:281-285.
6. Chattopadhyay I, Banerjee SS, Jha AK, Basu S. Effects of intrathecal dexmedetomidine as an additive to low-dose bupivacaine in patients undergoing transurethral resection of prostate. Indian J Anaesth. 2017; 61(12):1002-1008.
7. Kubre J, Sethi A, Mahobia M, Bindal D, Narang N, Saxena A, *et al*. Single dose intravenous dexmedetomidine prolongs spinal anaesthesia with hyperbaric bupivacaine. Anaesthesia, essays and researches. 2016; 10(2):273.
8. Hansda DP, Prakash DS, Haque D, Suwalka D. Block Characteristics and hemodynamic parameters following intra-thecal Hyperbaric 0.5% Bupivacaine with Dexmedetomidine and Hyperbaric 0.5% Bupivacaine alone in lower abdominal Surgeries. SEAJCRR. 2015; 4(2):1631-1641.
9. Paris A, Tonner PH. "Dexmedetomidine in anaesthesia". Current Opinion in Anaesthesiology 2005; 18(4): 412–8.
10. Thomas C Westfall, David P Westfall. Adrenergic agonists and antagonists, Goodman & Gilman's The Pharmacological Basis of Therapeutics: 12th edition, 277-288.
11. Kararmaz A, Kaya S, Turhanoglu S, Ozyilmaz MA. Low-dose bupivacaine-fentanyl spinal anaesthesia for TURP. Anaesthesia. 2003; 58:526-30
12. Wang YQ, Zhang XJ, Wang Y. Effect of intrathecal dexmedetomidine on cesarean section during spinal

anesthesia: a meta-analysis of randomized trials. Drug Des Devel Ther. 2019; 13:2933-2939. Published 2019 Aug 21.
13. Calasans-Maia JA, Zapata-Sudo G, Sudo RT. Dexmedetomidine prolongs spinal anaesthesia induced by levobupivacaine 0.5% in guinea-pigs. J Pharm Pharmacol. 2005; 57:1415-20.
14. Kim JE, Kim NY, Lee HS, Kil HK. Effects of intrathecal dexmedetomidine on low-dose bupivacaine spinal anesthesia in elderly patients undergoing transurethral prostatectomy. Biol Pharm Bull. 2013; 36:959-65
15. Talke PO, Caldwell JE, Richardson CA, Kirkegaard-Nielsen H, Stafford M. The effects of dexmedetomidine on neuromuscular blockade in human volunteers. Anesth Analg. 1999; 88:633-9
16. De Kock M, Gautier P, Fanard L, Hody JL, Lavand'homme P. Intrathecal ropivacaine and clonidine for ambulatory knee arthroscopy: A dose-response study. Anesthesiology. 2001; 94:574-8