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EFFECTS OF INTRATHECAL DEXMEDETOMIDINE ON LOW-DOSE BUPIVACAINE SPINAL ANAESTHESIA IN ELDERLY PATIENTS UNDERGOING TRANSURETHRAL PROSTATECTOMY

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ABSTRACT Transuretheral resection of prostate (TURP) for benign prostatic hyperplasia is frequently performed in elderly patients having cardiovascular limitations with various systemic diseases. Sixty patients classified in ASA I / II classes scheduled for TURP were studied. Patients were randomly allocated into study or control group. In our study, we found that 3µg of Dexmedetomidine added to 6mg of bupivacaine given intrathecally influences the sensory and motor block by shortening the onset time and prolonging the duration of absolute and effective analgesia without affecting the other parameters and complications of subarachnoid block. The onset of sensory block was faster in Study Group (D) with a mean value of 91.82±29.60 seconds as compared to a mean of 100.33± 11.29 seconds in the Control Group (S) and the difference was statistically significant. The motor block was also potentiated in the Dexmedetomidine group throughout the spinal anaesthesia. The duration of absolute and effective analgesia was notably prolonged in our study group with the mean duration being 173.00±22.49 and 255.500±26.10 respectively.

KEYWORDS : TURP, Spinal Anaesthesia, Dexmedetomidine, Bupivacaine

INTRODUCTION

Spinal anaesthesia is a common anaesthetic technique for patients undergoing transurethral resection of prostate (TURP). Most patients undergoing TURP are elderly and frequently have other co-morbidities.[1]Thus, it is important to limit the block level to minimize hemodynamic changes during the spinal anesthesia in such patients.[2] Low-dose local anesthetics can limit the block level and induce rapid recovery from anesthesia, but sometimes these low-dose local anesthetics may not provide an adequate anesthetic level for surgery. Intrathecal opioids or clonidine are frequently co-administered with local anesthetics ; the synergistic action of clonidine with local anesthetics is well established.[3] It has been investigated as the anxiolytic, sympatholytic, for analgesic properties related to α2-adrenoceptor binding and it is now being used as a co-analgesic drug. As an adjuvant, neuraxial administration is the most appropriate route for dexmedetomidine, because the analgesic effect of α2-agonists mostly occurs at spinal level, and dexmedetomidine's high lipophilicity facilitates rapid absorption into the cerebrospinal fluid and binding to the spinal cord α2-adrenoreceptor. Intrathecally administered dexmedetomidine has been shown to exert potent antinociceptive effects in animals.[4] To date, a few studies have been reported on the effects of intrathecal dexmedetomidine combined with local anesthetics in humans.[5]In those studies, using 10–15mg of bupivacaine, dexmedetomidine (3–15μg) prolonged the block duration of local anesthetics with a low-rate of side effects. Those studies, however, showed too high a block level (even up to T2) followed by a prolonged regression time .

We hypothesized that a small-dose of dexmedetomidine (3 μg) added to low-dose bupivacaine (6 mg) would produce an appropriate sensory block for TURP, rapid recovery from the limited motor block, and effective postoperative analgesia.

AIMS AND OBJECTIVES

1)To evaluate the adjuvant effects of intrathecal Dexmedetomidine in elderly patients undergoing transurethral prostate surgery.
2)To study the duration and regression of sensory and motor blockade of intrathecal Dexmedetomidine added to 0.5% (H) bupivacaine in transurethral prostate surgeries.

MATERIALS AND METHODS

Study Area: This randomized comparative study was conducted in the Department of Anesthesiology, Care Hospitals, Hyderabad .

Study Population: All male patients posted for TURP surgeries of age group 50-80 years of age. The proposed study was conducted over a period of six months (09/16 to 03/17).

Sample Size And Sample Technique: A total number of 60 patients (determined through power analysis) were evaluated to authenticate the study.

Sampling Technique: With simple random sampling technique, 60 patients were selected who fulfill the inclusion, exclusion criteria and were divided into two groups of 30 each.

Inclusion Criteria: Elderly male patients undergoing Transurethral resection of prostate.

Exclusion Criteria :
Refusal of the patient for study.
Patients of ASA grade III to IV.
Patients with uncontrolled hypertension.
Patients with hypersensitivity to study drugs.
Patients with coagulation disorders, hypervolemia, local or systemic infections and obvious spinal deformity.
Patients with heart block / dysrhythmia or neurological disorders.
Patients with severe hepatic failure because the clearance of dexmedetomidine is diminished to 32% of normal value

METHODOLOGY :

Sixty elderly patients undergoing TURP were included in this study. Using a random number sequence, patients were enrolled in one of the two group.

Group D (Dexmedetomidine group): Received intrathecal dexmedetomidine at dose of 3 mcg (0.3ml) with 6mg of 0.5% hyperbaric bupivacaine.

Group S (Saline group) : Will receive 6mg of hyperbaric bupivacaine with 0.3ml of preservative free normal saline.

Dexmedetomidine 100μg/mL was mixed with preservative free normal saline to get a concentration of 10μg/ml. 0.3mL of diluted Dexmedetomidine was added to the bupivacaine in-group D. Also, 0.3mL of preservative free normal saline was added to the bupivacaine in group S.

An independent investigator prepared the drug solutions and provided the coded drug to the anaesthetic administrator before the start of the anaesthesia.

Spinal Anaesthesia-
The fluid was minimally infused during the surgery to avoid over loading associated with the systemic absorption of irrigating fluid.

Spinal puncture was performed at L3-4 or L4-5 with a midline approach using a 27G Whitacre needle in the sitting position. After confirmation of free flow and clear cerebrospinal fluid, the drug was administered and the patients were then placed in the supine neutral position.

Assessment -
The primary end-point of this study was the time to regression of 2-sensory dermatomes from peak sensory block level. The secondary end-points were the motor block scales at peak sensory block and regression of 2-sensory dermatomes, as well as the postoperative analgesic requirement.

The block levels were checked on the bilateral mid-thoracic line with an ice cube and pinprick every 2 min from the drug injection. An ice cube assessed the cold peak block level and the sensory peak block level was assessed by pin- prick. The peak block level was defined as the same block level that persisted for four consecutive tests. For cases with a discrepancy in the dermatome level between the right and left sides, the higher level was selected. The degree of motor block was scored using the modified Bromage scale (Table-1). The sedation score was assessed every 15min for 1h using the Ramsay sedation scale (Table-2). Mean arterial pressure (MAP) and heart rate (HR) were measured every 5min for 20min. When the MAP or HR was decreased by 20% from the baseline, 4mg of ephedrine or 0.5mg of atropine was given intravenously. The peak block level, time to reach the peak block, motor block scale at peak sensory block, and supplemental analgesic requirement (tramadol 50mg) were recorded.

In the post anesthetic care unit (PACU), the time to the sensory regression of 2-dermatomes and motor block scales were recorded. After discharge from the PACU, the time to the first analgesic request (tramadol) was recorded. An independent investigator assessed the pain scales using the visual analog scale (VAS, 0–10) at the PACU (arrival and 30min) and at 1h, 2h, 3 and 4h after discharge from the PACU.

Table-1. Modified Bromage Scale

0	able to move the hip, knee, and ankle
1	unable to move the hip, but able to move the knee and ankle;
2	unable to move the hip and knee, but able to move the ankle
3	unable to move the hip, knee, and ankle

Table -2. Ramsay Sedation Score

1	anxious and agitated
2	cooperative and tranquil
3	drowsy but responds to command
4	asleep but responds to tactile stimulation
5	asleep and no response

Statistical Analysis
A master chart was prepared to arrange the observed parameters of each and every case. Mean and standard values were taken out. Statistical analysis was performed using Window stat Ver. 9.2 Inc. Data are presented as mean (S.D.), median, or numbers as appropriate. Patient characteristics were analyzed using the *t*-test, Modified *t*-Test, Variance ratio test, Welch's unequal variances test, Levene's Test, Brown- Forsythe Test.

Analysis of variance (ANOVA) of the data for the various parameters was done using student's paired t-test for intra group comparison and unpaired t-test for intergroup comparison.
Observations And Results

Table 3: Mean Age, Height, Weight and Duration of Surgery

Parameter	Group D	Group S	'p' Value
Age (in years) Mean ± Sd	64.43 ± 6.14	64.43 ± 6.14	> 0.05
Height (in cms)	164.83 ± 4.68	164.83 ± 4.68	> 0.05
Weight (in kgs)	66.8 ±7.86	66.8 ± 7.86	> 0.05
Duration OF surgery	43.33 ± 11.16	41.33 ±10.66	> 0.05

The mean age was comparable between the two groups; being 64.43 ± 6.14 in both group D and group S.

Similarly the height and weight of the subjects were also similar as shown in table 1.

The mean duration of surgery in-group D was 43.33 ± 11.16 and in-group S was 41.33 ± 10.66, which was comparable.

All patients in the study were ASA I or ASA II males, posted for Transurethral resection of prostate.

Table 4: Assessment of Sensory Block

Parameter	Group D	Group S	'p' value
Onset (sec)	91.83 ± 29.60	100.33 ± 11.29	> 0.05
Peak sensory level	T6: T8: T10 9: 17: 4	T6: T8: T10 0: 12: 18	
2 segment regression	110.83 ±12.60	82.50 ± 5.21	< 0.001
Duration of sensory block	163.66 ± 24.66	119.66 ± 7.97	<0.001

The above table depicts the assessment of sensory block after spinal anaesthesia in the study group (group D) and control group (group S) with their respective calculated probability (p).

As shown above the onset of anesthesia in both the groups were comparable with a 'p' value > 0.05. Onset of sensory block was **91.83 ± 29.60** sec and **100.33 ± 11.29** sec in-group D and S respectively. In majority of the cases the peak sensory level achieved was T6 – T8 in-group D and T10 in-group S.

Time taken for 2-segment regression was **110 ± 12.60** minutes in group D as compared to **82.50 ± 5.21** minutes in group S with a significant difference and a p value < 0.001.

The total duration of sensory block as measured by regression to level L1 was significantly longer in study group as compared to control group with a duration of **163.66 ± 24.66** minutes and **119.66 ± 7.97** minutes in group D and S respectively.

Table 5: Assessment of Motor Block

Parameter	Group D	Group S	'p' value
Onset (secs)	114.33 ± 36.35	114.16 ± 21.73	> 0.05
Time to achieve max. motor block (min)	3.8 ±0.92	4.43 ± 1.04	< 0.05
Duration of motor block (min)	204.33 ± 15.01	160.66 ± 8.06	< 0.001

This table gives the assessments of motor block after the spinal anaesthesia. The mean onset of motor block in Group S was **114.16 ± 21.73** seconds, while it was faster, **114.33 ± 36.35** seconds in group D and the difference was statistically significant.

Time to achieve maximum Bromage grade in Group S was 4.43 ± **1.04 minutes,** while in group D it was faster, **3.8 ± 0.92 minutes.** The difference was statistically highly significant.

The Duration of motor block was taken when Bromage grade became 0. It was **160.66 ± 8.06** minutes in Group S, while it was **204.33 ± 15.01** minutes in Group D. So it was significantly prolonged in group D compared to group S and the difference was statistically highly significant.

Intra-Operative Changes in Mean Pulse Rate

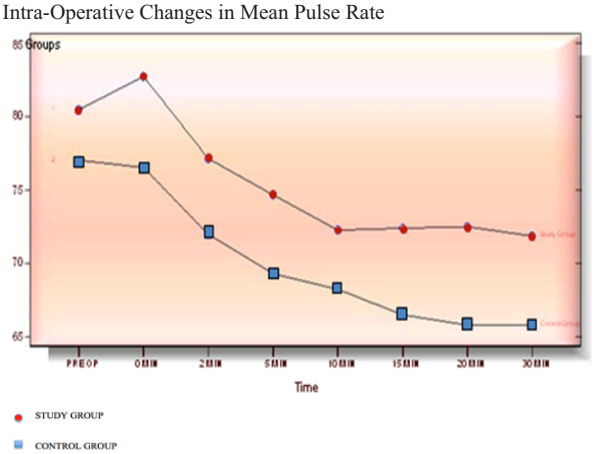

Figure 1: Comparison of intra-op mean pulse rate variation between group D and group S

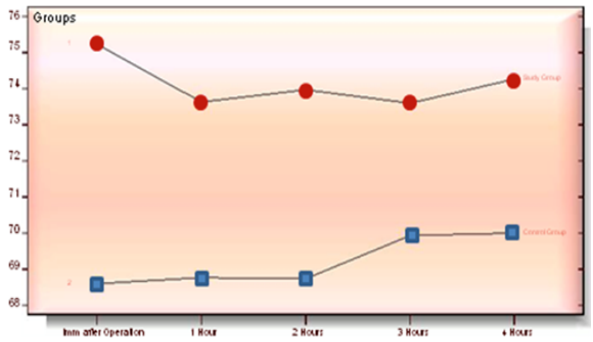

Figure 2: Comparison of post-op mean pulse rate variation between group D and group S

The line graph in figure 1 describes the variation in mean pulse rate as seen in the preoperative period and intraoperative period.

There is a steady fall in mean pulse rate following spinal anaesthesia and it continues until 10 mins into the intra operative period; in the study group (Group D). In the control group (Group S), the fall in mean pulse rate is more drastic and it continues to fall until 30 minutes into the intra operative period.

The line graph in figure 2 describes the mean pulse rate in the immediate postoperative period and 4 hours following the surgery. The study group shows a more stable mean pulse rate when compared to the control group, which continues to have a lower mean pulse rate and the variation among the group is statistically very significant.

Table 6: Intraoperative Variation in Blood Pressure (SBP and DBP)

(a) Systolic Blood Pressure (SBP):

TIME	Study Group(D)	Control Group(S)	Prob(p)
PRE OP	137.367 ± 2.577	139.400 ± 2.510	0.574
0 MIN	139.933 ± 2.724	140.400 ± 2.438	0.899
2 MIN	135.133 ± 2.723	133.967 ± 2.365	0.747
5 MIN	131.833 ± 2.463	127.833 ± 2.263	0.237
10 MIN	130.467 ± 2.636	124.000 ± 2.135	*0.062
15 MIN	128.500 ± 2.530	120.767 ± 2.043	*0.021
20 MIN	126.667 ± 2.472	119.200 ± 1.865	*0.019
30 MIN	127.133 ± 2.572	117.967 ± 1.822	*0.005
40 MIN	126.950 ± 3.561	116.368 ± 2.214	*0.017
60 MIN	133.625 ± 5.127	114.67 ± 3.018	*0.013
Imm Post Op	128.067 ± 2.205	118.700 ± 1.620	**0.001
1 Hour	128.00 ± 2.124	119.867 ± 1.649	**0.004
2 Hours	127.700 ± 2.206	120.967 ± 1.870	0.023
3 Hours	127.400 ± 2.171	122.367 ±1.805	0.080
4 Hours	127.867 ± 2.154	124.600 ± 1.752	0.244

[* = $p < 0.05$, ** = $p < 0.001$]

The table showed the changes in mean systolic blood pressure after spinal anaesthesia. In group D, intra group comparison showed significant fall in systolic blood pressure from 2 minutes after giving the block until 10 minutes; after which blood pressure remained so up to the end of the surgery and post operatively.

In group S the intra group comparison showed significant fall in systolic blood pressure at 2 minutes interval of giving block and persisted until 5 minutes, then the fall became highly significant, BP continued falling till the end of surgery and post operatively up to first 2 hours, and thereafter it became insignificant during postoperative period.

In inter group comparison by applying ANOVA; there is a statistically significant variation between the two groups up until 1-hour postoperative period.

Inter group comparison using ANOVA; showed no significant difference in Diastolic blood pressure between two groups.

Table 7: Duration of Absolute Analgesia

PARAMETER	GROUP D	GROUP S	'p' Value
Duration Of Absolute Analgesia (Min)	173 ± 22.49	129.833 ± 3.59	< 0.001

The table shows the duration of absolute analgesia in Group S was 129.833±3.59 minutes, while in group D it was 173±22.49 minutes. So the duration of absolute analgesia was prolonged in-group D than in group R and difference was statistically highly significant.

Table 8: Duration of Effective Analgesia

PARAMETER	GROUP D	GROUP S	'p' Value
Duration of effective analgesia (min)	255.50 ± 26.10	156.166 ± 10.72	< 0.001

The table shows the duration of effective analgesia in Group S was 156.166±10.72 minutes, while in group D it was 255.50±26.10 minutes. So the duration of effective analgesia was prolonged in group D than in group S and difference was statistically highly significant.

DISCUSSIONS

Spinal anaesthesia is the most preferred regional anaesthesia technique as it is easy to perform, produces rapid onset of anaesthesia and complete muscle relaxation and is also economical. The supplementation of bupivacaine spinal block with a low doses of intrathecal α2 agonists produce a significantly shorter onset of motor block and a significantly longer sensory and motor block than bupivacaine alone.[6]

The two groups in our study were comparable to each other with respect to age, ASA grading, type and duration of surgery and physical status. A study done by Kanazi et al. showed that the combination of 6 mg of intrathecal bupivacaine with a low dose (3 mcg) of Dexmedetomidine significantly shortened the onset of motor block and prolonged both motor and sensory block when compared with bupivacaine alone. In our study, we observed that the onset of **sensory block** was faster in Study Group (D) with a mean value of 91.82 ± 29.60 seconds as compared to a mean of 100.33 ± 11.29 seconds in the Control Group (S) and the difference was statistically significant. The sensory block was assessed in our study using pinprick method. This observation was in consonance with studies done by Kanazi et al [7]

The 2-segment regression time, which is the time to regression of 2-sensory dermatomes from the peak sensory block level, was the primary end point of our study. As observed in our study, the mean 2-segment regression time in study group was 110.83±12.60 minutes and that of control group was 82.50 ± 5.211 minutes and the difference between the two groups were highly significant ($p < 0.001$). Gupta. R et al[18] noted in their study that block regression was significantly slower with the addition of intrathecal Dexmedetomidine, as both time to two segment regressions and time to S2 regression were significantly more with intrathecal Dexmedetomidine.

The peak sensory level attained in the study group was also higher when compared to the control group and the difference was statistically significant ($p<0.001$). The duration of sensory block was also proved to be way longer in the Dexmedetomidine group as compared to the control group. In our study, **the motor block** was potentiated in the Dexmedetomidine group throughout the spinal anesthesia. With regard to onset of motor block we did not find any difference in our study or control group. But the time to achieve complete motor block and the duration of motor block was significantly better in the study group as compared to the control group. Mohammed AA et al[5] and Hala EA et al[9] also inferred through their studies that Dexmedetomidine prolongs not only the duration of sensory block, but also the degree and duration of the motor block. The potentiation mechanism of motor block by Dexmedetomidine is not well understood, but is suggested to be an additive or synergistic effect to the local anesthetics or related to the interference with neuromuscular activity[10], or binding of α2-agonists to motor neurons in the dorsal horn. The duration of absolute analgesia was calculated as the time from intrathecal injection of drug to first sensation of any pain at the site of surgery. This duration was notably prolonged in our study group

with the mean duration being 173.00 ± 22.49 minutes, while in the control group it was observed to be 129.83±3.59 minutes. The difference was significant statistically too with a p <0.001.

In our study mean heart rate remained more stable in study group when compared with the control group; which showed a more steeper fall in heart rate all through out intra op and it remained more or less stable in the post op. The systolic and diastolic BP showed a steadier course in the study group in contrast to the control group, which was statistically significant with a p value < 0.001. Kanazi et al observed in their patients that the addition of Dexmedetomidine or clonidine to bupivacaine did not cause a significant decrease in the blood pressure intra-operatively or post-operatively. Intrathecal local anesthetics block the sympathetic outflow and reduce the blood pressure. The sympathetic block is usually near maximal with the doses used for spinal anesthesia. The addition of a low dose of α_2-agonist to a high dose of local anesthetics does not further affect the near-maximal sympatholysis.[7]

In our study, there were no significant differences in sedation scores among groups. Intrathecally administered α2-agonists have a dose-dependent sedative effect. Al-Ghanem et al.[11] studied the effect of Dexmedetomidine 5 µg and 10µg with bupivacaine in urological procedures and found that Dexmedetomidine prolongs the duration of spinal anesthesia in a dose–dependent manner. Mohammed AA et al.[5] concluded that the time of the first rescue analgesic requirement was significantly prolonged in the Dexmedetomidine group. They also noted that the mean VAS scores showed a significant reduction immediately postoperatively and at 12 hours post- operatively in the Dexmedetomidine group. The mechanism may be due to an additive or synergistic effect secondary to the different mechanisms of action of local anesthetic and α2-adrenoceptor agonists .

Similarly in our study the mean time to first analgesic as calculated as effective analgesia was significantly prolonged in the study group as compared to the control group.

No intraoperative complications were noted in any of the patients during the course of the study.

SUMMARY

Various adjuvants have been used with local anaesthetics in spinal anesthesia to provide prolonged postoperative analgesia and to avoid intraoperative visceral and somatic pain. Dexmedetomidine, the highly selective α2 agonist drug was used as an adjuvant in this study. The aim of the study was to evaluate the adjuvant effects of dexmedetomidine and to study the onset duration and regression of the spinal block with addition of dexmedetomidine intrathecally. Sixty patients classified in ASA I / II classes scheduled for TURP were studied. Patients were randomly allocated into study or control group.

Patient characteristics were collected and subjected to ANOVA and t-test. After going through the study results, we inferred that the addition of dexmedetomidine quickens the onset and prolongs the duration of sensory block. The onset and time to achieve maximum motor block was fastened and duration of motor block was significantly prolonged. We noticed stable hemodynamics with minor fluctuations in blood pressure and heart rate throughout the perioperative period. Duration of absolute and effective analgesia was significantly prolonged. The number of rescue analgesics required in postoperative period was also significantly reduced. No incidences of complications in intra and postoperative period were noted.

CONCLUSION

In **conclusion**, our study showed that 3μg of Dexmedetomidine added to 6mg of bupivacaine given intrathecally influences the sensory and motor block by shortening the onset time and prolonging the duration of absolute and effective analgesia without affecting the other parameters and complications of subarachnoid block.

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