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COMPARATIVE EVALUATION OF TWO DIFFERENT DOSES OF INTRAVENOUS DEXMEDETOMIDINE (0.25MCG/KG AND 0.5MCG/KG) IN PROLONGING DURATION OF SPINAL ANAESTHESIA IN PATIENTS UNDERGOING TRANSURETHRAL RESECTION OF PROSTATE (TURP).

Anesthesiology

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ABSTRACT

Background: To compare the characteristics of spinal block, hemodynamic changes, and postoperative analgesia, following administration of intravenous dexmedetomidine (DMT) (0.25mcg/kg and 0.5mcg/kg) combined with low-dose Bupivacaine in elderly patients undergoing TURP.
Materials And Methods: This is a prospective, randomised, double blind study conducted out on hundred patients of either sex, aged 50-80 years, ASA grade I and II scheduled to Transurethral resection of prostate (TURP) under spinal anaesthesia.
Results: Maximum sensory block was achieved significantly earlier in Group D50 (10.64+2.75 min) as compared to group D25 (12.94+3.04 min), P=0.0012. Two segment regression of sensory block was found earlier in D25 groups (116.91+5.64 min) as compared to D50 group (135.73+8.27 min) and the difference was highly significant, P=0.00. Total duration of sensory block was found to be more in Group D50 (180+10.94 min) as compared to (159.41+6.715 min) in Group D25, P=0.00 . Recovery from motor block time ie; time to reach modified bromage score 0 was found earlier in Group D25 group (141.325+4.97mins) as compared to Group D50 (154.41+8.143 mins) which was highly significant.
Conclusion: We concluded that 0.5 mcg/kg of IV dexmedetomidine is significantly better (P<0.001) in terms of sensory, motor block characteristics and postoperative analgesic requirement as compared to 0.25mcg/kg while the incidence of hypotension, bradycardia, sedation, vomiting and dryness of mouth were comparable in both the groups.

KEYWORDS

Dexmedetomidine, TURP, Spinal anaesthesia, Old age, Sensory block

INTRODUCTION

Spinal anaesthesia is an established choice of anaesthesia for surgeries below the umbilicus. Spinal anaesthesia is the technique of choice in TURP.(1) Spinal anaesthesia has the advantage that it maintains spontaneous respiration during surgeries while providing necessary abdominal muscle relaxation for surgery.(2-3) Most of these patients coming for TURP are elderly with associated cardio-pulmonary, endocrine or other co-morbidities. Thus limitation of the level of sympathetic blockade due to spinal anaesthesia is necessary to minimize hemodynamic complications. Dexmedetomidine (DMT) is a sedative and analgesic, provide sedation and also helps in prolonging the postoperative analgesia (9-10) Dexmedetomidine is an imidazole compound, dextro isomer of medetomidine.

We hypothesized that a small dose of DMT (0.25mcg/kg and 0.5mcg/kg) given i.v. with low-dose Bupivacaine (8mg) intratheally would produce an appropriate sensory block for TURP, rapid recovery from the limited motor block, and effective postoperative analgesia. The aim of this study was to compare the characteristics of spinal block, hemodynamic changes, and postoperative analgesia, following administration of intravenous DMT (0.25mcg/kg and 0.5mcg/kg) combined with low-dose Bupivacaine spinal anaesthesia in elderly patients undergoing TURP.

MATERIALS AND METHODS

This study was conducted in the department of Anaesthesiology in National Institute of Medical Sciences and Research for duration of 18 months from January 2019 to June 2020 after taking approval of the institutional ethical committee and informed consent of each patient. It was conducted on hundred patients of either sex, aged 50-80 years, ASA grade I and II scheduled for Transurethral resection of prostate (TURP) under spinal anaesthesia.

Study Design:
Prospective, randomised, double blind clinical study.

Sample size: 100 patients.

Sample Size Calculation:
Sample size was calculated using software Epi InfoTM 7, with the assumption of alpha error to be 5% and beta error to be 20% i.e. 95% confidence interval and 80% power of study. Assumption of exposed group taken to be 95% with 10% margin of error. Thus a sample size of 100 patients was taken with 50 patients in each group.

Subjects & Selection Method:
All participants were randomly divided into two groups (Group D25 and Group D50) by a computer generated randomization table.

Group D25: Patients received I.V. DMT 0.25mcg/kg in dilution of 10 ml over 5 minutes, immediately after spinal anaesthesia with 0.5% hyperbaric bupivacaine 1.3 ml (8mg).

Group D50: Patients received I.V. DMT 0.5mcg/kg in dilution of 10 ml over 5 minutes, immediately after spinal anaesthesia with 0.5% hyperbaric bupivacaine 1.3 ml (8mg).

Inclusion Criteria:
1. Patients with age 50-80 years
2. ASA grade I/II with no known drug allergy.

Exclusion Criteria:
1. ASA grade III and IV
2. Known case of sinus bradycardia
3. History of Coagulopathy
4. Severe mitral stenosis
5. Aortic stenosis
6. Skin infection at spinal sites.

Technique Methodology:
After preloading the patients with Ringer Lactate 15ml/kg, patient taken in sitting position and lumber puncture was performed at L3-L4 level with Quincke type 25 gauge spinal needle and injection bupivacaine 1.3ml (8mg) solution was injected intrathecally over 30 seconds. As per group allocation Injection DMT 0.25mcg/kg or 0.5mcg/kg in dilution of 10 ml was given by infusion pump over 10 mins, immediately after spinal anaesthesia.

Data Recording:
Height of sensory block was assessed by pin-prick test in mid axillary

line. Motor block was assessed by modified bromage score (0 to 3). Any fall in the heart rate below 50 beats/minute was considered as bradycardia and treated with incremental doses of Injection intravenous (IV) atropine 0.3mg. Systolic arterial blood pressure below 100 mmHg or 20% fall from baseline, or both was considered as hypotension and treated with Inj. Mephentermin 6 mg incremental boluses. Sedation score was assessed by Ramsey sedation score (RSS).Post-operative pain intensity was assessed using VAS scale at 2, 6, 10, 12, 24 hour (hr) and Injection Tramadol 50 mg as rescue analgesic once VAS score >3 was given.

The time to two segment sensory regression and time to motor recovery that is time to reach to modified bromage scale of 0 were also evaluated.

If patient complained of pain during surgery, it was considered as failure of SAB and Inj.Fentanyl 2 mcg/kg was given as bolus and if necessary supplementation with General anaesthesia was done. Patient requiring Inj. Fentanyl supplementation or G.A. was not included for statistical analysis.

Statistical Analysis:

Data was presented as mean, standard deviation, median (range), or percentage, as appropriate. Study data was entered into the SPSS software (version 21, SPSS) and was analysed with the chi-square test for qualitative and student t-test for quantitative variables, between the trial and control groups, P values less than 0.05 was considered significant.

RESULTS

Table 1 Demographic Comparison Of Both Group

	Group D50 (n=50)	Group D25 (n=50)	P value
Mean age (years)	67.72±6.84	65.56±6.4	0.11(NS)
Mean weight (kg)	59.08±8.74	60.08±7.09	0.53(NS)
ASA grade(I/II)	42/8	43/7	0.78(NS)
Duration of surgery (minutes)	69±20.95	62.5±13.52	0.06(NS)

*P<0.05 is significant(S), P<0.001 is highly significant (HS), Non significant(NS)

Table 1 shows there was no statistically significant difference in the demographic characteristics like age, weight, ASA grading and duration of surgery in two groups. (p>0.05)

Table 2 Comparison Of Hemodynamic Parameters In Two Groups

		Group D50 (n=50)	Group D25 (n=50)	P value
Heart rate (BPM)	Preoperative HR	86.7±13.88	84.2±15.57	0.65 (NS)
	Mean of lowest HR	64.06±12.3	67.6±13.14	0.17 (NS)
	Time taken to achieve lowest HR (min)	28.86±17.29	26.6±21.23	0.56(NS)
S.B.P. (mm of Hg)	Preoperative SBP	132.04±12.9 9	135.78±12. 62	0.147(NS)
	Mean of lowest SBP	111.98±11.3 1	110.4±14.9 5	0.55(NS)
	Time taken to achieve lowest SBP (min)	22.22±17.58	25.7±18.25	0.34(NS)
D.B.P. (mm of Hg)	Preoperative DBP	81.54±9.09	77.88±8.76	0.869(NS)
	Mean of lowest DBP	69.98±7.89	69.68±10.2 5	0.87(NS)
	Time taken to achieve lowest DBP (min)	23.55±19.58	23.02±17.2 4	0.88(NS)
M.A.P. (mm of Hg)	Preoperative MAP	88.06±11.79	98.96±0.2	0.36(NS)
	Mean of lowest MAP	77.06±11.14	78.64±9.08	0.44(NS)
	Time taken to achieve lowest MAP (min)	26.82±18.75	27.16±21.1 3	0.93(NS)

We observed that mean value of lowest HR in Group D50 and D25 were comparable (P=0.17) and time taken to achieve lowest HR was also comparable (P=0.56).

Mean value of lowest SBP,DBP and MAP were recorded in Group D50 & Group D25 but the difference did not reach statistical significance (P=0.34,0.88 and 0.93 respectively). Mean value of time taken for lowest SBP, DBP and MAP were also comparable (P=0.55, 0.87 and 0.44 respectively).

Table 3 Characteristic Of Sensory Block

	Group D50 (min)	Group D25 (min)	P value
Onset of sensory level(T10)	2.74±0.72	2.78±0.86	0.80 (NS)
Time to reach highest sensory block(T6)	10.48±2.57	12.40±4.43	0.009 (HS)
Time to two segment regression of sensory block	135.3±8.42	116.7±5.77	0.000 (HS)
Total duration of sensory block	179±11.07	158.8±6.51	0.000 (HS)

*P<0.05 is significant(S), P<0.001 is highly significant (HS), Non significant (NS)\

Table 3 shows characteristic of sensory block in the groups. Onset of sensory block was earlier in Group D25 (2.78+0.86) as compared to Group D50 (2.74+0.72 mins).

Maximum sensory block was achieved significantly earlier in Group D50 (10.48+2.57 min) as compared to group D25 (12.40+4.43 min), P=0.009. Two segment regression of sensory block was also found earlier in D25 groups (116.7+5.77 min) as compared to D50 group (135.3+8.42 min) and the difference was highly significant, P=0.00.

Total duration of sensory block was found to be more in Group D50 (179+11.07 min) as compared to (158.8+6.51 min) in Group D25, P=0.00 which was highly significant between the groups.

Table 4 Characteristic Of Motor Block

	Group D50 (min)	Group D25 (min)	P value
Time for modified bromage score 3	10.48±1.89	12.7±3.23	0.000 (HS)
Time for modified bromage score 0	154±7.82	141.3±4.93	0.000 (HS)

*P<0.05 is significant(S), P<0.001 is highly significant (HS), Non significant (NS)

Table 4 shows characteristic of motor block between the groups.
Group D50 patients achieved Bromage score 3 earlier (10.48+1.89 min) as compared to (12.7+3.23 min) in group D25 (P=0.00).

Recovery from motor block time ie; time to reach modified bromage score 0 was found earlier in Group D25 group (141.3+4.93mins) compared to Group D50 (154+7.82) mins which was highly significant.

Table 5 Comparison Of Modified Ramsey Sedation Score

	Group D50	Group D25	P value
Intraoperative	2.43±0.24	1.81±0.05	0.0001 (HS)
Postoperative	1.41±0.16	1.07±0.13	0.000 (HS)

*P<0.05 is significant(S), P<0.001 is highly significant (HS), Non significant (NS)

Table 5 shows comparison of Modified RSS between the groups in intraoperative and postoperative period.

Patient in Group D50 reported higher sedation than group D25 and the difference was highly significant throughout the perioperative period.

Table 6 Time To First Rescue Analgesic Dose And Total Rescue Dose And Number Of Dose

	Group D50	Group D25	P value
Time to first rescue dose (min.)	268.4±53.03	171.8±11.24	0.000 (HS)
Total rescue dose (mg)	137.5±26.85	240±23.69	0.000 (HS)
Total no. of dose	2.66±0.48	4.6±0.57	0.000 (HS)

*P<0.05 is significant(S), P<0.001 is highly significant (HS), Non significant (NS)

Table 6 demonstrates that time of requirement of first rescue analgesia (Inj. Tramadol 100 mg) was delayed in Group D50 as compared to Group D25 (P-0.000).

Postoperatively analgesic requirement in terms of number of doses and total dose in mg was higher in Group D25 as compared to D50 and the difference was statistically highly significance (P=0.00).

Table 7. Comparison Of Postoperative Vas Score

Time (hours)	Group D50	Group D25	P value
4	2.48±1.47	4.66±0.48	0.000(HS)
10	2.32±1.87	2.06±2.07	0.51 (NS)
12	1.88±2.07	3.16±2.32	0.004 (HS)
24	4.12±0.33	4.82±0.39	0.000(HS)

*P<0.05 is significant(S), P<0.001 is highly significant (HS), Non significant (NS).

Table 7 shows comparison of Vas Score in 24 hours postoperative between the groups.

In Group D25 reported more pain at 4 hrs compared to Group D50 (VAS- 4.66+0.48 vs 2.48+1.47) which was highly significant at 12 and 24 hours. Group D50 had lower VAS compared to Group D25 which was significant at 12 hours and highly significant at 24 hours.

Table 8. Management Of Hypotension And Bradycardia

		Group D50		Group D25		P value
		Mean+SD	N	Mean+SD	N	
Mephentermine (No. of dose)		1.25+0.5	7	1.67+0.41	9	0.0857
		1-2		1-2		
Mephentermine Total dose (mg)		7.5+3	7	7+2.45	9	0.718
		6-12		6-12		
Atropine (No. of dose)	Mean	1	6	1	6	1.00 (NS)
	Range	1-1		1		
Atropine total dose	Mean	0.6	6	0.6	6	1.00 (NS)
	Range	0.6-0.6		0.6-0.6		

Table 8 demonstrates that requirement of mephentermine in terms of number of doses and total dose in mg was comparable in both groups (P=0.0857 and P=0.718 respectively).

Similarly, there was no significant difference in requirement of atropine in terms of number of doses (P=1.00) and total doses in mg (P=1.00) in the two groups.

Table 9. Comparison Of Intraoperative Adverse Effects

Side effects	Group D50	Group D25	P value
N/H+	13(26%)	9(18%)	0.33 (NS)
Vomiting	13(26%)	7(14%)	0.13 (NS)
Hypotension	9 (18%)	6(12%)	0.40(NS)
Hypertension	0(0%)	0(0%)	
Brady cardia	6(12%)	6(12%)	1.00
Restless ness	2(4%)	2(4%)	1.00
Shortness of breath	0(4%)	0(0%)	
Dryness of mouth	2(4%)	0(4%)	0.15 (NS)
Chest Pain	0(0%)	0(0%)	
Headache	0(0%)	0(0%)	

*P<0.05 is significant(S), P<0.001 is highly significant (HS), Non significant (NS)

Table 9 shows that most common intraoperative adverse effect was vomiting 26 (n=13) in Group D50 and 18 (n=9) in Group D25, P=0.13. Incidence of hypotension and bradycardia and dryness of mouth was comparable. 18% (n=9) patients of Group D50 experienced hypotension as compared to 12%% (n=6) patients in Group D25 showing significant difference (P=0.40).

DISCUSSION

Transurethral resection of the prostate (TURP) is the most common surgical intervention for patients with benign prostatic hyperplasia. Spinal anaesthesia is the technique of choice in TURP.(2)Spinal anaesthesia has the advantage of being able to maintain spontaneous breathing as well as relaxing the necessary muscles for surgery.(3-4) It also provides post-operative analgesia, reduces blood loss during surgery and prevents the need for tracheal intubation that may irritate the airway leading to coughing and straining and may exacerbate postoperative haemorrhage.

Although awake patient in regional anaesthesia has theoretical advantages, such as earlier detection of TURP syndrome but the time limit and patient's anxiety for anaesthesia and surgery and discomfort in lithotomy position after spinal anaesthesia presents certain disadvantages.

Adequate sedation in spinal anaesthesia relieves the anxiety of the patient, improves physiological and psychological stress, and increases the satisfaction of both the surgeon and patient. (3-4) On the other hand excessive sedation not only masks the early signs of TURP syndrome but also produces postoperative delirium in elderly patients. So the aim of sedation with spinal anaesthesia in TURP should be to provide a cooperative and arousable patient with cardiopulmonary stability.(14)

Dexmedetomidine is a sedative, hypnotic, analgesic, and to a certain extent can cover up inadequate block height and has minimal respiratory depressant effect. (1)

Demographic data (Table 1)
On analysis of the demographic profile both the groups were found to be comparable regarding age, weight, ASA (I,II)grade and duration of surgery.

Quality of block (Table 3,4)
Intravenous dexmedetomidine prolongs the motor and sensory block of bupivacaine by an additive or synergistic effect of both of them. Intravenous dexmedetomidine acts by depressing the release of C-fibers transmitters through binding to presynaptic C fibers and by hyperpolarization of postsynaptic dorsal horn neurons.

Maximum sensory block was achieved significantly earlier in Group D50 (10.64+2.75 min) as compared to group D25 (12.94+3.04 min), P=0.0012. Two segment regression of sensory block was found earlier in D25 groups (116.91+5.64 min) as compared to D50 group (135.73+8.27 min) and the difference was highly significant, P=0.00 which could be attributed to the lower doses of dexmedetomidine in D25 showing a positive additive or synergistic effect of higher doses of dexmedetomidine as seen in D50. Total duration of sensory block was found to be more in Group D50 (180+10.94 min) as compared to (159.41+6.715 min) in Group D25, P=0.00 which was highly significant between the groups when motor block was assessed between the groups when motor block was assessed between the groups, Group D50 patients achieved Bromage score 3 earlier (10.735+1.797 min) as compared to (12.794+2.52 min) in group D25 (P=0.00). Recovery from motor block time ie; time to reach modified bromage score 0 was found earlier in Group D25 group (141.325+4.97mins) as compared to Group D50 (154.41+8.143 mins) which was highly significant.

Similar to our study Jung SH et al (2013)(31) had conducted a study where they compared two different doses of dexmedetomidine (0.25 & 0.5 mcg/kg) to control group and found that two-dermatome sensory regression time was significantly increased in dexmedetomidine groups. The duration of motor and sensory anaesthesia was significantly increased in group 0.5mcg/kg. But maximum level of block was not found different in three groups.

More P. et al (2017)(16) did not found any significant difference in time to achieve highest sensory block in dexmedetomidine group as compared to normal saline group but duration of sensory block , two segment regression of sensory block and regression of MBS 0 was significantly prolonged in group D as compared to group C which supported our study. They also noted earlier achievement of MBS 3 in dexmedetomidine group as compared to control but the difference was not significant.

Similar to our study Annamalai A. et al (2013)(24) also found that IV dexmedetomidine given before and 30 mins after intrathecal administration of bupivacaine prolongs the duration of sensory blockade and increases the maximum level of block during spinal anaesthesia when compared with control group however duration of motor block was found similar in all the groups.

Abdallah FW et al (2013)(26) in a systematic review and meta analysis

found that IV dexmedetomidine can prolonged the duration of sensory block by at least 34% (point estimate 8%), and motor block duration was prolonged by at least 17% (point estimate 21%),P<0.00001 when compared with placebo.

Lee MH et al (2014)(22) used two different doses of dexmedetomidine (0.5 mcg/kg and 1 mcg/kg) 10 mins before SAB and found that two segment regression times of sensory block and time for regression of motor block was prolonged in dexmedetomidine group but contrary to our study they did not find statistically significant differences in duration of spinal anaesthesia between the D-1 and the D-0.5 groups.

Harsoor SS et al (2013)(25) gave dexmedetomidine (0.5mcg/kg) 10 mins prior to SAB and found faster onset of sensory block and prolongation in time for two segment regression of sensory block. Motor block was also found to be faster in onset and slower in regression when compared with control group. But in their study they used infusion of dexmedetomidine throughout the surgery.

In contrast Kaya et al (2010)(28) also reported that the use of single dose of 0.5 mcg/kg of dexmedetomidine did not affect the duration of motor block.

Sedation (Table 5)
Sedation produced by dexmedetomidine is like that of natural sleep as it act on the locus cereleus of the brain, which induces sedation resembling natural sleep by means of sleep modulation and maintaining respiratory control.(1)

Group D50 reported significantly higher sedation than group D25 both intraoperatively and postoperatively in our study.

In contrast Jung HR (2013)(31) et al found that there was no significant difference in sedation scores with two different doses of dexmedetomidine(0.25 & 0.5 mcg/kg).

Harsoor SS et al (2013) (25) found higher intraoperative sedation with dexmedetomidine when compared the control group but postoperative sedation scores were comparable in their study.

Lee MH et al (2014)(22) also reported higher sedation score in group given higher doses of dexmedetomidine (1 mcg/kg) as compared to 0.5 mcg/kg.

Postoperative analgesia (Table 6,7)
Dexmedetomidine inhibits the release of substance P from the dorsal horn of spinal cord, leading to primary analgesic effects which was well proven in our study by different parameters assessed for postoperative analgesia.

Most of the studies compared the effects of dexmedetomidine either IV or IT to control group and found dexmedetomidine was an effective analgesic and prolonged duration of analgesia and time for first rescue analgesia.

a) Time for first rescue analgesia (Table 6)
In our study we compared two different doses of dexmedetomidine and found that time for need of first rescue analgesia (Inj. Tramadol 100 mg) was delayed in Group D50 than in Group D25 (P=0.000). Postoperatively analgesic requirement in terms of number of doses and total dose in mg` was higher in Group D25 as compared to D50 and the difference was statistically highly significance (P=0.00). Dinesh et al (32) also reported prolongation in time for request of first rescue analgesic and 24 hours mean analgesic requirement lesser in dexmedetomidine group compared to control group. Similarly Reddy et al (33)when compared intravenous dexmedetomidine with clonidine before spinal anaesthesia observed longer interval for first rescue analgesic in dexmedetomidine group.

b) VAS score (Table 7)
In our study, Group D25 reported more pain at 4 hrs compared to Group D50 (VAS- 4.66+0.48 vs 2.48+1.47) which was highly significant at 12 and 24 hours Group D50 had lower VAS as compared to Group D25 which was significant at 12 hours and highly significant at 24 hours.

Abdallah et al (26) revealed that use of intravenous dexmedetomidine produces 60% reduces in pain score at 6 hrs. Annamalai et al (24) has used 1 mcg/kg dexmedetomidine as slow bolus over 10 min, either 10 min before or 30 min after the spinal anaesthesia with bupivacaine reported reduced pain score and longer duration of postoperative analgesia by dexmedetomidine. Kaya FN et al (28) reported no significant difference in VAS score between the groups postoperatively at 4, 12, 24 hours.

CONCLUSION

We concluded that 0.5 mcg/kg of IV dexmedetomidine is significantly better (P<0.001) in terms of sensory, motor block characteristics and postoperative analgesic requirement as compared to 0.25mcg/kg while the incidence of hypotension, bradycardia, sedation, vomiting and dryness of mouth were comparable in both the groups.

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