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Research Article

# Efficacy of intrathecal dexmedetomidine in prevention of shivering in patients undergoing transurethral prostatectomy: A randomized controlled trial



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## KEYWORDS

Shivering;  
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prostatectomy;  
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Dexmedetomidine

**Abstract** *Background:* Shivering is a frequent complication following spinal anesthesia (SA). It is more common in transurethral resection of the prostate (TURP) that may be due to absorption of large amount of irrigating fluids. We aimed to investigate the role of intrathecal dexmedetomidine in attenuation and prevention of shivering in patients undergoing TURP under SA.

*Methods:* In a randomized, controlled trial, eighty patients were scheduled for elective TURP under SA. Patients were randomly allocated into two groups: control group (group C): patients received 2.5 ml of hyperbaric bupivacaine 0.5% plus 0.5 ml of normal saline and dexmedetomidine group (group D); patients received 2.5 ml of hyperbaric bupivacaine 0.5%, plus 10 µg dexmedetomidine in 0.5 ml of normal saline. Hemodynamic parameters, shivering score and any adverse effects were recorded.

*Results:* The incidence of shivering was significantly reduced in group D, 6/40 patients (15%) compared with 23/40 patients (57%) in group C ( $P < 0.001$ ). The frequency of bradycardia, hypotension, number of patients treated with meperidine and ephedrine were significantly higher in group D compared with group C ( $P = 0.048$ ,  $P = 0.043$ ,  $P = 0.011$ ,  $P = 0.043$ ) respectively. There was insignificant difference in the incidence of nausea, vomiting and TUR syndrome in patients in both groups ( $p > 0.05$ ).

*Conclusion:* Our results suggest that the use of 10 µg intrathecal dexmedetomidine in patients undergoing TURP has a noticeable control of shivering even in occurrence of tolerable side effects.

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## 1. Introduction

Shivering is a frequent complication following SA [1]. The incidence of shivering has been reported to be about 36–85% after SA [2]. It is more common in TURP that may be due to

absorption of large amount of irrigating fluid at room temperature [3]. Shivering may occur as a response to hypothermia. However, it may also occur in normothermic patients [4]. SA impairs the thermoregulation system by inhibiting tonic vasoconstriction below the level of anesthesia through sympathetic and somatic neural blockade [5]. With internal redistribution of heat from the core to the peripheral compartment, the loss of thermoregulatory vasoconstriction results in increased heat loss from body surfaces in excess of metabolic heat production [5]. Shivering causes patient discomfort, interruption of monitoring, increases O<sub>2</sub> consumption, CO<sub>2</sub> production, and catecholamine secretion that increase cardiac output, heart rate, and blood pressure [6].

Many medications have been tried to prevent or reduce shivering but the ideal one has not been determined yet. Meperidine was tried alone or in combination with clonidine and urapidil [7]. Magnesium sulfate [8], ketamine, fentanyl and morphine have been tried with no convincing results [9].

Dexmedetomidine is highly selective Alpha ( $\alpha$ )-2-adrenergic receptor agonist and is approved to decrease the shivering threshold. It has sedative, analgesic, sympatholytic, anesthetic-sparing and hemodynamic-stabilizing properties. Addition of intrathecal dexmedetomidine to heavy bupivacaine 0.5% was more advantageous than fentanyl with special regard to its analgesic properties in diabetic surgical patients [10,11]. Premedication with IM dexmedetomidine reduces the incidence of postoperative shivering [12]. Few studies have been done to evaluate the efficacy of intrathecal dexmedetomidine in attenuation and prevention of shivering in TURP [13].

We aimed to investigate the role of intrathecal dexmedetomidine in attenuation and prevention of shivering in TURP under SA in a randomized controlled trial.

## 2. Patients and methods

After local Ethics Committee approval, written, informed consent was obtained from all patients participating in this randomized, double-blinded, controlled trial. Eighty patients, aged 40–70 years, ASA physical statuses I, II, and III scheduled for elective TURP under SA, were enrolled in this study. Transrectal ultrasound (TRUS) was done for all patients for detection of prostatic size. Exclusion criteria included: patients with contraindications to SA, allergy to the study medication, thyroid disease, Parkinson's disease and patients receiving vasodilators or medications likely to alter thermoregulation. Patients with unstable coronary artery diseases, 2nd and 3rd degree heart block, congestive heart failure, tight mitral or aortic valve stenosis and ventricular tachyarrhythmia were also excluded from the study. Past and current medical records were checked for associated medical disorders and concomitant medication intake. Preoperative serum sodium and hemoglobin concentration were checked. In the pre-anesthesia room I.V. line was inserted and intravenous preload with isotonic saline solution was infused to all patients at 10 ml/kg within 30 min. Afterward the rate of isotonic saline solution infusion was set at 5 ml/kg/h. Patients in both groups were premedicated with 1–3 mg midazolam intravenously. In the operating room basic monitoring of ECG, oxygen saturation by pulse oximetry and noninvasive blood pressure were applied to all patients and recorded at 5 min intervals using standard

monitors (AS/3; Datex Ohmeda, Bromma, Sweden). Core body temperature was recorded of all patients on arrival to the operating room using a tympanic thermometer then at 15 min intervals. Operating room (OR) temperature was maintained at 22–24 °C. All patients were covered with one layer of surgical drapes over the chest, thighs, and calves during the operation. Core temperature below 36 °C was considered hypothermia.

Under aseptic technique, subarachnoid block was performed in sitting position using 25 G spinal needle at either the L3–L4 or L4–L5 intervertebral spaces. Patients were randomly allocated by the use of sealed envelope assignment into two groups: control group (group C): patients received 2.5 ml of hyperbaric bupivacaine 0.5%, plus 0.5 ml of normal saline and dexmedetomidine group (group D); patients received 2.5 ml of hyperbaric bupivacaine 0.5%, plus 10 µg preservative free dexmedetomidine (Precedex; Hospira Inc., Lake Forest, Illinois, USA) in 0.5 ml of normal saline. The study medications were prepared by an anesthesiologist blinded to the study. Also SA, data measurements and recording were carried out by an anesthesiologist blinded to the study. Supplemental oxygen (5 L/min) was delivered via face mask during surgery time. After injection of local anesthetic, the assessment of sensory block level was done using pin-prick test (needle prick) to be above T10 dermatome. Patients with incomplete or failed SA were subsequently excluded from the study and received general anesthesia (GA). TURP was performed using a continuous flow resectoscope with monopolar cautery using 1.5% glycine as an irrigant solution. All intravenous and irrigation fluids were warmed to 37 °C in warming cabinets. Shivering was assessed by Crossley and Mahajan scale [14] where 0 = No shivering, 1 = Cyanosis and piloerection, 2 = Visible tremors only in one muscle group, 3 = Visible tremors in more than one muscle group, and 4 = intense shivering, tremors of the head, arm. During surgery, shivering score was assessed and recorded at 15 min intervals. If shivering score was  $\geq 3$ , meperidine 25 mg was administered intravenously. The number of patients treated for shivering with meperidine was recorded. Occurrence of signs and symptoms of TUR syndrome (blurring of vision, irritability, confusion, convulsion, etc.) was reported. Any adverse effects such as bradycardia, hypotension, nausea and vomiting were recorded. Bradycardia was defined as a decrease in heart rate below 50 beat/min. Bradycardia was treated with IV bolus of atropine 0.5 mg. Hypotension was defined as a decrease in MAP of more than 20% from baseline. Hypotension was treated with IV boluses of ephedrine 5–10 mg. The number of patients treated for hypotension with ephedrine was recorded. If patients developed nausea or vomiting, IV bolus of metoclopramide 10 mg was administered. Total volume of irrigation solution used for each patient was recorded by the end of surgery. In the postanesthesia care unit (PACU), ambient temperature was maintained at 25 °C to 26 °C and all patients were covered with one layer of drapes and one cotton blanket. Heart rate (HR), mean arterial blood pressure (MAP), oxygen saturation, core body temperature and shivering scores were recorded to all patients at 15 min intervals over one hour postoperatively in PACU. Serum Na and hemoglobin concentration were checked once postoperatively. Anesthesia time, surgery time (resection time) and any adverse events were also recorded.

### 3. Statistical analysis

The sample size was calculated using the G Power analysis program version 3.1. The incidence of shivering related to SA from previous reports was 55% [15]. The sample size required to achieve 40% reduction was minimum 33 patients in each group with a power of 80% and  $\alpha = 0.05$ . Eighty patients were included for the possibility of drop out cases.

Data were analyzed using SPSS (Statistical Package for Social Sciences) version 15. Qualitative data were presented as number and percent. Comparison between groups was done by Chi-Square test. Quantitative data were presented as mean  $\pm$  SD. Student *t*-test was used to compare between two groups.  $P < 0.05$  was considered to be statistically significant.

### 4. Results

The two groups were comparable regarding age, BMI, anesthesia and surgery times, prostatic size and amounts of irrigation solution (Table 1). HR and MAP were comparable between both groups at different times of measurement intra-operatively and in PACU ( $P > 0.05$ ) but significant difference was noted within the groups after SA when compared with baseline values ( $P < 0.05$ ) (Figs. 1 and 2). While maintaining the ambient temperature in the operating room between 22 and 24 °C, the average baseline core body temperature for group C was  $37.00 \pm 08$  and for group D was  $37.01 \pm 10$  ( $p > 0.05$ ). At the end of TURP procedure it was  $35.29 \pm 19$  for group C and  $35.31 \pm 22$  for group D ( $p > 0.05$ ). At one hour postoperatively while maintaining the ambient temperature in the PACU between 25 and 26 °C, core temperature for group C was  $36.27 \pm 32$  and for group D was  $36.40 \pm 33$  ( $p > 0.05$ ). Core temperature was significantly reduced after SA compared with baseline values within the groups ( $P < 0.05$ ) (Fig. 3). Based on Crossley and Mahajan scale the incidence of shivering was significantly reduced in group D compared with group C ( $p < 0.001$ ) where 6/40 patients (15%) in group D developed shivering (four patients with grade 1 and two patients with grade 2) while 23/40 patients (57%) in group C developed shivering (ten patients with grade 1, seven patients with grade 2 and six patients with grade 3). No patient in both groups developed grade 4 shivering (Table 2). No significant difference as regards preoperative and postoperative values of hemoglobin and serum sodium ( $P > 0.05$ ) was obtained (Table 3). The frequency of bradycardia (6 patients vs. one patient), hypotension

(8 patients vs. 2 patients), number of patients treated with meperidine (6 patients vs. no patient) and ephedrine (8 patients vs. 2 patients) were significantly higher in group D compared with group C ( $P = 0.048$ ,  $P = 0.043$ ,  $P = 0.011$ ,  $P = 0.043$ ) respectively (Table 4). There was no significant difference in the incidence of nausea, vomiting and TUR syndrome in patients in both groups ( $p > 0.05$ ) (Table 4). No patient in both groups had respiratory depression or needed GA due to failed SA (see Fig. 4).

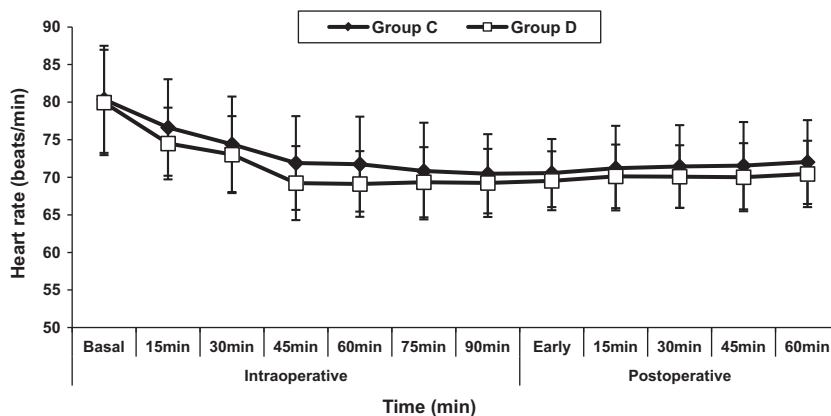
### 5. Discussion

The thermoregulatory mechanism in human body is a complex one that normally keeps the temperature within a tight range (36.5–37.5 °C) known as “inter-threshold range”. If the core temperature decreases below that range, the body responds by vasoconstriction and shivering which increases heat production two to five folds [16]. Thus, shivering is a protective mechanism to preserve body heat but no definite linear relationship exists between body temperature and occurrence of shivering [17]. SA induces inhibition of vasoconstriction below the level of anesthesia through sympathetic and somatic blockade with subsequent vasodilatation and increases cutaneous blood flow that results in increasing heat loss via the skin [18]. In contrast to these changes, vasoconstriction and shivering are restricted to the upper body during SA [8]. The exact mechanism of shivering during SA has not been fully established. The possible mechanisms include cessation of central thermoregulation, internal redistribution of body heat and heat loss to the environment [13]. Shivering which is a rhythmic contraction of a group of muscle has anesthetic and surgical drawbacks. It increases O<sub>2</sub> consumption and CO<sub>2</sub> production with subsequent increase in basal metabolic rate. Shivering interferes with patient’s monitoring and it may be a problem in old patients who is undergoing TURP as most of them have one or more associated comorbidities with limited cardiac and respiratory reserve. It may also lead to urethral injury, induce more bleeding and be associated with uncomfortable surgery [19]. Shivering is mostly a response to hypothermia [20]. However, it may be seen in normothermic patients under SA [2]. Risk factors for hypothermia in spinal anesthesia are aging, level of sensory block, and temperatures of the local anesthetic, operating room and intravenous solutions [8,13]. In the current study, the temperature of the operating room was maintained at 22–24 °C. Intravenous and irrigation solutions were also maintained at 37 °C during surgery. Pharmacological therapies, such as opioid peptides, tramadol, physostigmine,

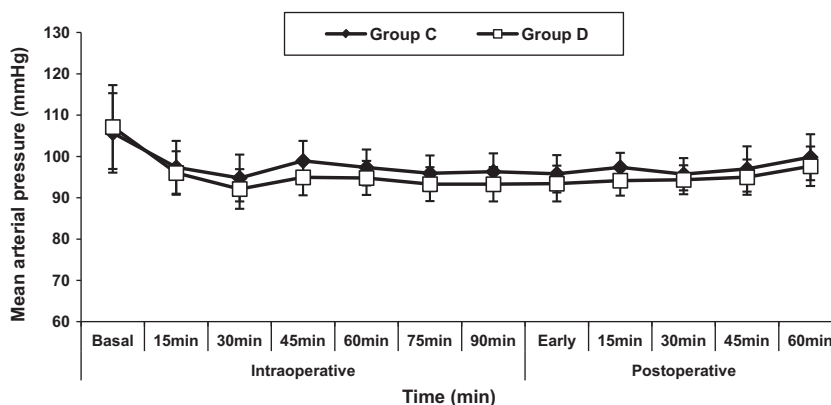
**Table 1** Patient characteristics, prostatic size (g), amount of irrigant solution (liter/patient) anesthesia and surgery time (minutes) among studied groups.

Variables	Group C (n = 40)	Group D (n = 40)	P-value
Age (years)	59.40 $\pm$ 7.21	60.65 $\pm$ 7.97	0.464
BMI (kg/m <sup>2</sup> )	25.97 $\pm$ 1.81	25.42 $\pm$ 1.44	0.136
Prostatic size (g)	54.58 $\pm$ 6.15	55.65 $\pm$ 6.08	0.434
Anesthesia time (min)	106.83 $\pm$ 5.58	108.40 $\pm$ 9.99	0.388
Surgery time (min)	79.88 $\pm$ 8.20	78.87 $\pm$ 3.55	0.482
Irrigation solution (liter/patient)	52.18 $\pm$ 3.82	50.58 $\pm$ 4.89	0.107

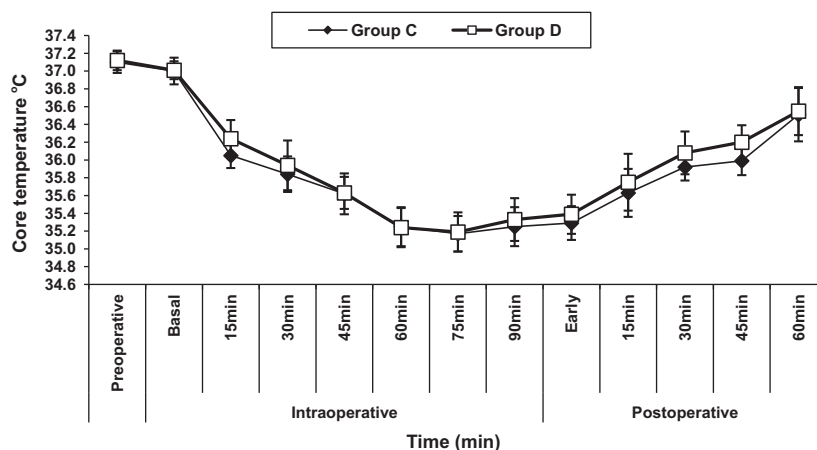
Group C: Control group, group D: Dexmedetomidine group, n: number. Data are presented as mean  $\pm$  SD.



**Figure 1** Intraoperative and postoperative heart rate changes (beats/min) among groups. Data are presented as mean ± SD. Group C: Control group, group D: Dexmedetomidine group.



**Figure 2** Intraoperative and postoperative mean arterial blood pressure changes (mmHg) among groups. Data are presented as mean ± SD. Group C: Control group, group D: Dexmedetomidine group.



**Figure 3** Perioperative core body temperature changes (°C) among groups. Data are presented as mean ± SD. Group C: Control group, group D: Dexmedetomidine group.

clonidine, ketamine, and magnesium sulfate, have been used to prevent shivering [7,13]. Meperidine is among opioids, which is extensively studied due to its anti-shivering effect. Disadvantages of meperidine include nausea, vomiting and respiratory depression. Fentanyl and morphine could control shivering

but it should be given in large doses to be effective with increase of the incidence of side effects [21]. Tramadol may cause nausea, vomiting and respiratory depression during and after SA. The hypertensive and tachycardic effects of ketamine may limit its use [8]. Magnesium sulfate also has been



**Table 2** Preoperative and postoperative values of hemoglobin (Hg) g/L and serum sodium (Na) mmol/L among studied groups.

Variables	Group C (n = 40)	Group D (n = 40)	P-value
Preoperative Hg (g/L)	128.30 ± 12.10	125.80 ± 12.40	0.364
Postoperative Hg (g/L)	110.90 ± 10.20	109.50 ± 09.80	0.540
Preoperative sodium (mmol/L)	137.93 ± 2.96	138.18 ± 3.05	0.711
Postoperative sodium (mmol/L)	128.03 ± 3.77	128.48 ± 3.34	0.574

Group C: Control group, group D: Dexmedetomidine group, n: number.  
Data are presented as mean ± SD.

**Table 3** Intraoperative and postoperative number and percentage of patients with different shivering scores among studied groups.

Shivering score	Group C (n = 40)	Group D (n = 40)	P-value
0	17 (42.5%)	34 (85%)*	<0.001
1	10 (25%)	4 (10%)	0.077
2	7 (17.5%)	2 (5%)*	0.077
3	6 (15%)	0 (0%)*	0.011
4	0 (0%)	0 (0%)	–

Group C: Control group, group D: Dexmedetomidine group, n: number.

Data are presented as number and percentage.

\* Significant difference compared with group C.

tried to control postoperative shivering but its mechanism of action is uncertain and also it has side effects such as nausea, vomiting, feeling warm, flushing; it may induce respiratory depression [22]. Dexmedetomidine is highly selective  $\alpha_2$  adrenergic receptors agonist. It is approved to have sedative, analgesic, perioperative sympatholytic, anesthetic-sparing, and hemodynamic-stabilizing properties [10]. It is highly lipophilic, the fact that may facilitate its rapid absorption into the cerebrospinal fluid and binding to the spinal cord  $\alpha_2$  adrenoceptors [23]. The quality of the spinal anesthesia has been reported to be improved by the addition of dexmedetomidine [10] with less hypotensive effect and an added sedative effect without respiratory depression [13]. Activation of  $\alpha_2$  adrenergic receptors in the brain and spinal cord by dexmedetomidine decreases sympathetic tone and attenuates the neuroendocrine and hemodynamic responses to anesthesia and surgery. Thus, dexmedetomidine can mediate both the beneficial and unwanted effects of shivering provoked by hypothermia, such as increased catecholamine concentrations, oxygen consumption, blood pressure, and heart rates [13]. In the current study, the patients in dexmedetomidine group shivered less (6/40)

(15%) with lower grades of shivering (two patients grade 2 and four patients grade 1) and no patients received meperidine to stop shivering compared with higher grades (six patients grade 3, seven patients grade 2 and ten patients grade 1), higher incidence (23/40) (57%) of shivering and 6 patients received meperidine to stop shivering in control group. In a prospective controlled study upon 60 patients that evaluated the effect of dexmedetomidine on shivering during SA, Usta et al. reported a similar results, 3/30 (20%) in dexmedetomidine group and 17/30 (56%) in the control group developed shivering ( $p = 0.001$ ) [13].

In agreement with our results, Coskuner et al. [24] reported significant decrease in shivered patients in dexmedetomidine group, with a significant increase in patients experiencing bradycardia that was safely treated with atropine. In a placebo-controlled study upon 120 patients that evaluated the efficacy of dexmedetomidine compared with meperidine and placebo in preventing postanesthesia shivering after elective abdominal or orthopedic surgery, Bicer and colleagues [25] reported that, 22 patients (55%) in the placebo group, four patients (10%) in the meperidine group and six patients (15%) in the group D developed shivering. They concluded that intraoperative dexmedetomidine 1  $\mu\text{g}/\text{kg}$  administered intravenously reduces postanesthesia shivering as does meperidine 0.5 mg/kg in patients after major surgery. These results support the results of the current study. Also, in a prospective controlled study upon 90 patients that evaluated the effect of dexmedetomidine on postoperative shivering in patients undergoing elective abdominal hysterectomy, Elvan and colleagues [26] reported a similar results, 7/45 (15%) in dexmedetomidine group and 21/45 (46%) in saline group developed shivering ( $P = 0.001$ ). The incidence of bradycardia that safely treated with atropine was higher in dexmedetomidine group. In agreement with our results, a randomized controlled trial upon 62 patients that evaluated the role of dexmedetomidine 5  $\mu\text{g}$  added to heavy bupivacaine 0.5% intrathecally for lower abdominal surgeries, reported lower incidence of shivering in

**Table 4** Incidence of adverse effects and number of patients received meperidine and ephedrine among studied groups.

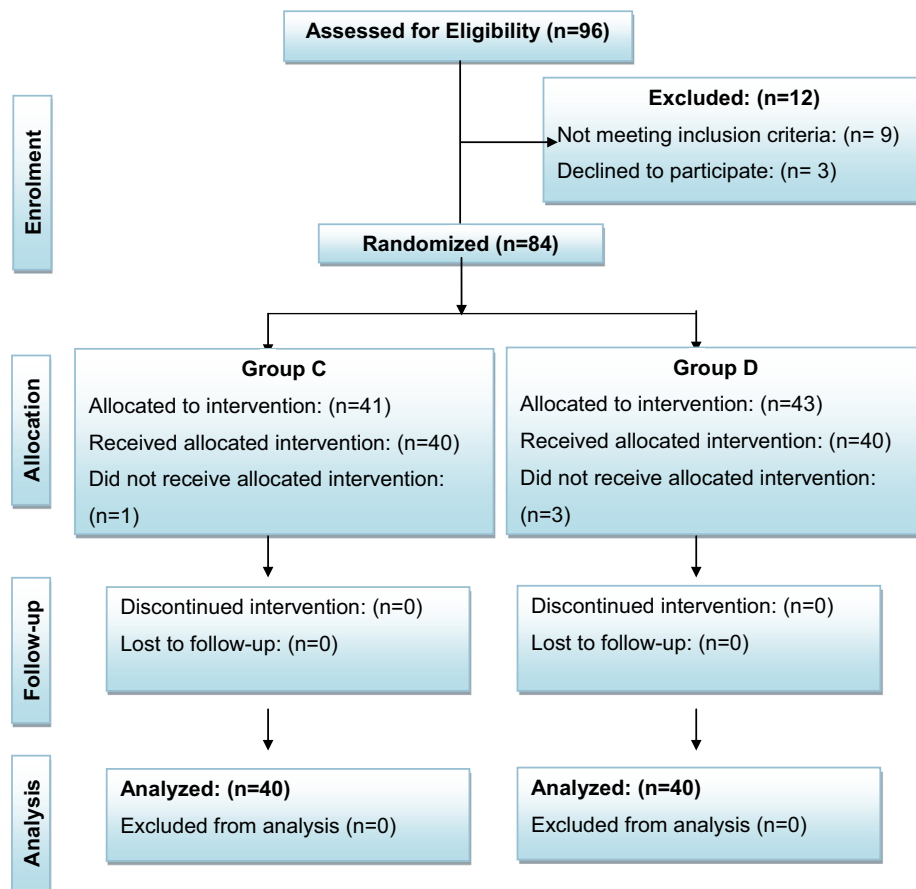
Variables	Group C (n = 40)	Group D (n = 40)	P-value
Patients with bradycardia	1 (2.5%)	6 (15%)*	0.048
Patients with hypotension	2 (5%)	8 (20%)*	0.043
Patients with nausea and vomiting	2 (5%)	2 (5%)	1.0
Patients with TUR syndrome	2 (5%)	1 (2.5%)	0.556
Patients received meperidine	6 (15%)	0 (0%)*	0.011
Patients received ephedrine	2 (5%)	8 (20%)*	0.043

Group C: Control group, group D: Dexmedetomidine group, n: number.

Data are presented as number (percentage).

\* Significant difference ( $p < 0.05$ ) compared with group C.

Randomization according to consort 2010:



Group C: control group, Group D: dexmedetomidine group.

**Figure 4** Randomization according to consort 2010.

dexmedetomidine group (2/31) compared with (12/31) in control group. Bradycardia was observed more (8/31) among patients in dexmedetomidine group while no patient in control group experienced bradycardia [27]. In the current study, HR and MAP started to decrease after SA in both groups at different times of measurement. This decrease however was not statistically significant between both groups but was lower in group D. The bradycardia and hypotension observed in dexmedetomidine group were tolerable and safely treated without rebound effect in accordance with other reports [13,28]. The incidence of nausea, vomiting and TUR syndrome was insignificant between both groups in accordance with other reports [8,13,17]. In this study, no patients in both groups had respiratory depression or needed GA due to failed SA.

A limitation of this study, the time to shivering was not estimated and we did not assess different doses of dexmedetomidine; further studies are needed to evaluate the effects of dexmedetomidine with various doses.

## 6. Conclusion

Our results suggest that the use of 10 µg intrathecal dexmedetomidine in patients undergoing TURP has a noticeable control of shivering even in occurrence of tolerable side effects.

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## Conflict of interest

No conflict of interest emerged during the implementation of this work. The paper had not been presented at any congress before.

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