

## Comparison the Effects of Oral Tizanidine and Tramadol on Intra- and Post-operative Shivering in Patients Underwent Spinal Anesthesia

### Abstract

**Background:** Heat loss and core-to-peripheral redistribution of body heat occur in patients undergoing neuraxial anesthesia resulted to decrease of core temperature and early reach of shivering threshold. Because shivering has deleterious metabolic and cardiovascular effects, it should ideally be prevented by pharmacologic or other means. Tizanidine is an alpha-2 agonist. We evaluated the usefulness of oral tizanidine (TI) and tramadol in preventing of shivering in patients undergoing spinal anesthesia for transurethral resection of the prostate (TURP). **Materials and Methods:** Ninety patients, scheduled for TURP with spinal anesthesia, were prospectively enrolled. Patients were randomly assigned to 1 of 3 groups. 90 min before spinal anesthesia, 30 patients received 4 mg oral TI, 30 patients received 50 mg tramadol, and 30 patients received placebo as control group. Spinal anesthesia was induced at the L3–L4 or L4–L5 interspaces with 12.5 mg bupivacaine. An investigator blinded to the drugs recorded the frequency and degree of shivering. **Results:** The overall frequency and severity of shivering were significantly lower in patients treated with TI and tramadol compared to placebo ( $P = 0.04$ ) ( $P = 0.001$ ). There was not much difference in the nausea and vomiting of both the drugs ( $P = 0.26$ ) ( $P = 0.11$ ). There was no difference in hemodynamic parameters between three groups ( $P = 0.08$ ) ( $P = 0.13$ ). **Conclusions:** Oral TI and tramadol were comparable in respect to their effect in decreasing the incidence, intensity shivering when used prophylactically in patients who underwent TURP with spinal anesthesia.

**Keywords:** Shivering, spinal, tizanidine, tramadol

### Introduction

Postoperative shivering has been seen in 40% of cases. However, it seems that this incidence has been decreased due to maintenance of normothermia during surgery and the use of opiates.<sup>[1]</sup> The findings showed that increased body metabolism during shivering can lead to myocardial ischemia.<sup>[2]</sup> Postoperative shivering can increase intracranial and intraocular pressure and through inducing tenderness lead to postoperative pain.<sup>[3]</sup>

Shivering incidence during neuraxial block may be reduced by warming the body surface skin.<sup>[4]</sup> The drugs including Meperidine (25 mg intravenous),<sup>[5]</sup> Clonidine (75 mg intravenous solution), Ketanserin (10 mg intravenous),<sup>[6]</sup> Dexmedetomidine<sup>[7]</sup> and Magnesium sulfate (30 mg intravenous)<sup>[8]</sup> are effective for tremor after anesthesia and neuraxial block. Opioids such as meperidine have been used to treat and prevent postoperative

shivering.<sup>[9-12]</sup> However, some side effects such as respiratory depression, low blood pressure, nausea, and vomiting have limited the use of opiates after surgery.<sup>[13]</sup> Tramadol is associated with lower risk of respiratory disease, drug tolerance and drug dependence for the treatment and prevention of shivering.<sup>[14-16]</sup> Various studies have been conducted on the effects of intravenous tramadol on treatment and prevention of postoperative shivering.<sup>[17]</sup> Alpha-2 agonists as antihypertensive drugs can improve sleep disorders, anxiety, and pain.<sup>[18]</sup>

Tizanidine (TI) is an oral alpha-2 agonist and mediates central muscle relaxant activity for the treatment of painful muscle spasms. Moreover, less cardiovascular side effects of TI compared to other medications make it an important and useful alternative in anesthetics.<sup>[19]</sup>

Patients undergoing transurethral resection of the prostate (TURP) due to other underlying disease such as cardiovascular

Leili Adinehmehr,  
Sohrab Salimi<sup>1</sup>,  
Mohammad Azad  
Majedi<sup>2</sup>,  
Azadeh Alizadeh<sup>3</sup>,  
Shahryar Sane<sup>3</sup>

From the Department of Anesthesiology, Shahid Beheshti Hospital, Isfahan University of Medical Sciences, Isfahan, <sup>1</sup>Department of General Anesthesiology, Imam Hossein General Hospital, Shahid Beheshti University of Medical Sciences, <sup>2</sup>Department of Anesthesiology, Kurdistan University of Medical Sciences, Sanandaj, <sup>3</sup>Department of Anesthesiology, Imam Khomeini Hospital, Urmia University of Medical Sciences, Urmia, Iran

### Address for correspondence:

Dr. Shahryar Sane,  
Department of Anesthesiology,  
Imam Khomeini Hospital,  
Urmia University of Medical  
Sciences, Urmia, Iran.  
E-mail: shahryarsane@yahoo.  
com

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disease and aging have many problems. Hypothermia in these patients can be associated with complications such as myocardial ischemia.<sup>[20]</sup> Therefore, the aim of this study was to evaluate the effect of oral TI, tramadol, and placebo on intra- and post-operative shivering in patients undergoing TURP with spinal anesthesia.

## Materials and Methods

### Study population

This randomized, double-blind clinical trial study was conducted on patients undergoing TURP in Imam Khomeini Hospital. In the current study, the number of patients according to the previous study<sup>[21]</sup> was considered 90. Moreover, this study was approved by Urmia University of Medical Sciences [Figure 1].

### Eligibility criteria

Inclusion criteria were patients 40–60 years old with the American Society of Anesthesiologists Classification I and II undergoing TURP and exclusion criteria were obesity,

sensitivity to tramadol or TI, ischemic heart disease history, thyroid and cerebrovascular disease, diabetic autonomic neuropathy, contraindication for regional anesthesia, and duration of surgery more than 1.5 h. Moreover, patient taking vascular medications were excluded from the study.

The first patient received tramadol, the second patient TI and the third patient placebo. The first group received 4 mg oral TI, the second group 50 mg tramadol and other group placebo 90 min before surgery. The colleague of the operating room was unaware of the patient classification. Another person analyzed the data based on the collected forms and personal profile data. All patients before surgery were fasting for at least 8 h. Prostatectomy surgery was performed in an operating room with the same temperature and humidity.

In the operating room, pulse oximetry monitoring, noninvasive blood pressure, and electrocardiogram were used for all patients.

In the current study, all patients received injection of 12.5 mg 0.5% hyperbaric bupivacaine through spinal

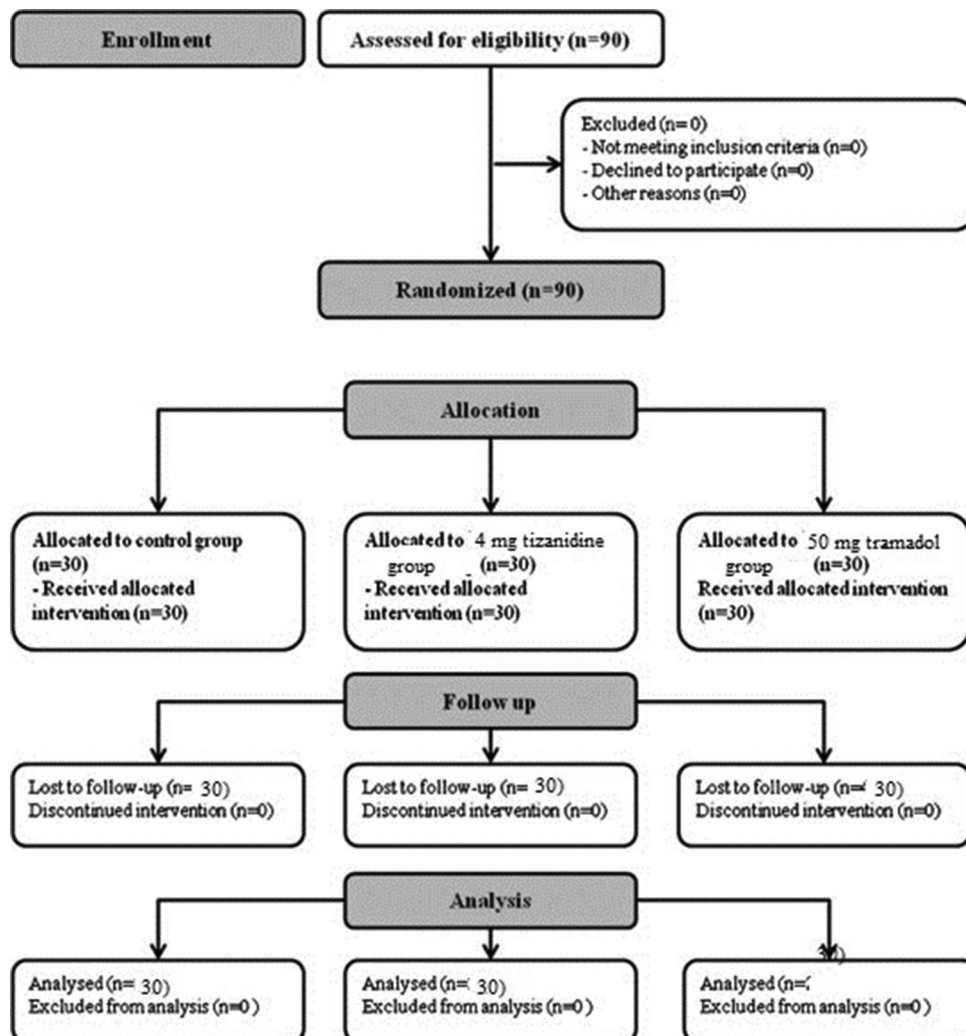


Figure 1: CONSRT flowchart

anesthesia in sitting position at the L3–L4 interspaces with a 25 G Quincke bevel needle. The level of spinal anesthesia was achieved to T9–T10. The temperature of fluid bladder washing in all patients was the same (36°C). The incidence of nausea, vomiting and severity of shivering during surgery and recovery were recorded. Heart rate, mean arterial pressure, respiratory rate, arterial oxygen saturation, and skin surface temperature were measured and recorded at the beginning and then every 10 min during the operation. If systolic pressure drop (more than 20% of the base) intravenous ephedrine was used as a vasopressor. In patients who develop shivering, intravenous meperidine (25 mg) should be used.

- 0 - No shivering
- 1 - Mild Fasciculations of face or neck
- 2 - Visible tremor involving more than one muscle group
- 3 - Gross muscular activity involving the entire body.<sup>[22]</sup>

### Statistical analysis

Data were entered into SPSS version 16 (SPSS Inc., Chicago, Ill., USA). Fisher's exact test, ANOVA, and repeated measures was used for analysis of data. Moreover, data were expressed as mean  $\pm$  standard deviation.

### Results

The mean age of patients receiving tramadol (TR), TI and placebo (P) was  $51.86 \pm 5.70$ ,  $54.2 \pm 5.65$ , and  $55.36 \pm 5.26$  years old, respectively. Table 1 shows the mean age and body mass index (BMI) among three groups. As shown in Table 1, there was no significant difference among three groups in terms of age and BMI ( $P > 0.05$ ).

Table 2 shows the frequency of shivering in three groups during surgery and recovery.

There was a significant difference among three groups in terms of shivering ( $P = 0.04$ ). Moreover, no significant difference was seen between TR group with placebo and TI group with  $P$  in terms of shivering during surgery ( $P = 0.11$ ). According to Fisher's exact test, significant difference was seen between TI group and  $P$  in terms of shivering during recovery ( $P = 0.02$ ). Furthermore, significant difference was observed between TR group and  $P$  in terms of shivering during recovery ( $P = 0.05$ ), while this difference was not significant between TR group and TI group ( $P = 0.5$ ).

Table 3 shows severity of shivering in three groups.

According to ANOVA test, significant difference was observed among three groups in terms of severity of shivering ( $P = 0.001$ ). No significant difference was observed between TR group and TI group with respect to severity of shivering ( $P = 0.80$ ). However, significant difference was observed between TR group with  $P$  ( $P = 0.001$ ) and TI group with  $P$  in terms of severity of shivering ( $P = 0.001$ ).

Table 4 shows the frequency of nausea and vomiting in all groups during surgery and recovery.

According to Fisher's exact test, there was no significant difference between TI group and  $P$  in terms of nausea during surgery ( $P = 0.11$ ) and recovery ( $P = 0.05$ ). No significant difference was seen between TR group and  $P$  with respect to nausea during surgery ( $P = 0.5$ ) and recovery ( $P = 0.23$ ). Moreover, no significant difference was seen between TR group and TI group with respect to nausea during surgery ( $P = 0.5$ ) and recovery ( $P = 0.12$ ).

Furthermore, there was no significant difference between TI group and  $P$  in terms of vomiting during surgery ( $P = 0.11$ ) and recovery ( $P = 0.05$ ). No significant difference was seen between TR group and  $P$  with respect to vomiting during surgery ( $P = 0.3$ ) and recovery ( $P = 0.33$ ). Moreover, no significant difference was seen between TR group and TI group with respect to vomiting during surgery ( $P = 0.11$ ) and recovery ( $P = 0.24$ ).

The mean arterial pressure before and during surgery (90 min) in three groups is shown in Table 5.

**Table 1: The mean age and body mass index among three groups**

Variable	Placebo	Tizanidine	Tramadol	$P$ (ANOVA test)
Mean age (year)	$55.36 \pm 5.26$	$54.2 \pm 5.56$	$51.86 \pm 5.70$	0.5
BMI (kg/m <sup>2</sup> )	$26.32 \pm 3.5$	$25.27 \pm 2.2$	$26.25 \pm 3.25$	0.2

BMI: Body mass index

**Table 2: Frequency of shivering in three groups**

Group	Shivering during recovery		Shivering during surgery	
	No (%)	Yes (%)	Yes (%)	No (%)
Tramadol	27 (90)	3 (10)	30 (100)	0
Tizanidine	28 (93.3)	2 (6.7)	30 (100)	0
Placebo	21 (70)	10 (30)	27 (90)	3 (10)
Total	76 (84.4)	14 (15.6)	87 (96.7)	3 (3.3)

**Table 3: Severity of shivering in three groups**

Variables	Placebo	Tizanidine	Tramadol	$P$
Severity of shivering	$2.88 \pm 0.42$	$2.08 \pm 0.3$	$1.66 \pm 0.57$	0.001

**Table 4: Frequency of nausea and vomiting in all groups**

Group	Vomiting		Nausea	
	During recovery (%)	During surgery (%)	During recovery (%)	During surgery (%)
Tramadol	0	3 (10)	2 (6.7)	4 (13.3)
Tizanidine	2 (6.7)	0	6 (20)	0
Placebo	0	1 (3.3)	3 (10)	3 (10)
Total	2 (2.2)	4 (4.4)	11 (12.2)	7 (7.8)

According to repeated measures, there was no significant difference between the mean arterial pressure before and during surgery in three groups ( $P = 0.08$ ).

The mean heart rate before and during surgery (90 min) in three groups is shown in Table 6.

According to repeated measures, no significant difference was observed among three groups in terms of heart rate ( $P = 0.13$ ). Table 7 shows the mean arterial oxygen saturation before and during surgery.

According to repeated measures, no significant difference was seen among three groups with respect to arterial oxygen saturation before and during surgery ( $P = 0.43$ ). Table 8 shows the mean temperature in three groups before and during surgery.

According to repeated measures, no significant difference was observed among three groups in terms of the mean temperature ( $P = 0.12$ ).

## Discussion

This study was conducted in operating room of Imam Khomeini Hospital during 1.5 years. Intra- and post-operative shivering is very unpleasant and annoying for patients and can lead to multiple complications. Today, the prevention and treatment of intra- and post-operative

shivering is as important as the treatment of pain, and various methods and medications are used in this regard, but no method or an ideal drug has yet been identified. Tramadol is an opioid and it exerts its effect mainly through  $\mu$  receptors. However, kappa and delta receptors are used less by tramadol. Moreover, it activates descending pain inhibitory pathways in the spinal cord. The mechanism of anti-shivering effect of tramadol is through serotonergic and noradrenergic receptors.

Obviously, prevention is preferable than treatment and causes the patient do not experience an unpleasant state of postoperative shivering.<sup>[11]</sup> Alpha-2 adrenergic agonists are now extensively used in anesthesia and critical care. Alpha-2-adrenergic agonists through binding to alpha-2 receptors cause vasoconstriction and decrease shivering. They also act on the thermoregulatory center (temperature control) in the hypothalamus.<sup>[15,22]</sup> The results of this study showed that oral TI and Tramadol before surgery decrease intra- and post-operative shivering in patients underwent spinal anesthesia, while there was no significant difference among three groups in terms of some parameters including nausea, vomiting, and hemodynamics. The heart rate of patients in TI group was significantly lower than other groups in recovery.

Shukla *et al.*, in 2011 evaluated the effects of intravenous clonidine and tramadol on postoperative shivering in

**Table 5: The mean arterial pressure before and during surgery in three groups**

The mean arterial pressure	Placebo	Tizanidine	Tramadol
Before surgery	96.64±11.62	95.04±10.91	98.81±10.69
10 min	90.15±10.58	86.63±17.07	92.24±12.36
20 min	94.37±8.27	91.83±8.51	94.62±11.05
30 min	93.06±8.78	91.74±9.22	92.37±10.09
40 min	93.28±10.31	92.79±9.41	93.23±9.73
50 min	91.21±10.55	89.05±10.12	93.04±11.08
60 min	90.61±10.12	90.49±9.78	93.36±9.16
70 min	91.82±7.28	88.66±9.16	89.60±7.64
80 min	91.39±7.18	85.96±9.64	89.56±5.71
90 min	91.48±5.40	91.04±6.53	95.79±3.39

**Table 6: The mean heart rate before and during surgery in three groups**

Heart rate (bpm)	Placebo	Tizanidine	Tramadol
Before surgery	78.63±13.22	75.83±11.45	78.26±10.08
10 min	78.60±10.57	78.40±9.86	79.03±7.09
20 min	78.43±10.75	76.60±6.40	77.93±7.05
30 min	77.70±11.15	74.70±9.24	77.90±8.11
40 min	78.26±8.56	73.83±9.24	76.66±8.11
50 min	77.76±9.38	75.46±12.15	75.66±8.30
60 min	75.13±8.94	74.13±9.13	76.03±8.62
70 min	75.70±7.70	73.76±7.42	75.56±7.42
80 min	74.20±8.24	72.53±5.10	76.20±8.41
90 min	71.53±7.20	68.66±4.38	76.76±8.43

**Table 7: The mean arterial oxygen saturation before and during surgery**

The mean arterial oxygen saturation	Placebo	Tizanidine	Tramadol
Before surgery	97.90±1.74	97.76±1.65	98.30±1.72
10 min	98.30±1.26	97.96±1.58	98.80±0.88
20 min	98.43±1.13	98.13±1.27	98.86±1.25
30 min	96.56±11.30	98.20±1.21	98.56±1.22
40 min	94.69±15.74	98.40±1.37	98.80±1.12
50 min	98.50±1.19	97.83±5.58	99.13±0.97
60 min	98±0.64	98.53±1.25	97.80±2.12
70 min	97.53±0.77	97.83±0.74	96.90±5.36
80 min	98.46±0.81	98.43±0.85	98.10±0.40
90 min	98±0.92	98.26±0.82	98.83±0.83

**Table 8: The mean temperature in three groups before and during surgery**

The mean temperature (C)	Placebo	Tizanidine	Tramadol
Before surgery	36.02±0.29	36.94±0.12	36.59±9.14
10 min	36.93±0.31	36.94±0.13	36.92±0.41
20 min	36.89±0.30	36.94±0.15	36.90±0.20
30 min	36.69±0.22	36.93±0.17	36.84±0.18
40 min	37.05±0.37	36.95±0.11	36.88±0.24
50 min	36.93±0.11	36.94±0.13	36.89±0.31
60 min	36.90±0.13	36.80±0.20	36.88±0.27
70 min	36.86±0.39	36.96±0.11	36.73±0.42
80 min	36.84±0.16	36.78±0.31	36.75±0.10
90 min	36.98±0.03	36.97±0.04	36.78±0.09

patients underwent spinal anesthesia. They reported that the loss of shivering was faster in clonidine group than tramadol group, although no significant difference was observed between two groups in terms of shivering.<sup>[21]</sup> Clonidine is more effective than tramadol for controlling body temperature. Moreover, clonidine has less side effects than tramadol. Furthermore, shivering is lower in TI group than other groups in our study. Tewari *et al.*, in 2014 demonstrated the effect of 50 mg oral tramadol on decreasing shivering during TURP surgery with spinal anesthesia.<sup>[22]</sup> Moreover, they compared the effects of oral clonidine and tramadol for preventing shivering in patients underwent TURP with spinal anesthesia and found that both tramadol and clonidine were effective in reducing the severity and duration of shivering.<sup>[23]</sup>

Mittal *et al.*, in 2014 evaluated the effects of dexmedetomidine and tramadol on hemodynamic and shivering after spinal anesthesia. They concluded that both drugs are effective on shivering rate, nausea, and vomiting. The alpha-2 agonist drug used in our study was TI, in which we did not evaluate the decrease rate of shivering incidence. However, the incidence of shivering decreased in both groups. The incidence of nausea and vomiting was lower in the TI group than other groups, but this difference was not significant.<sup>[24]</sup>

Heidari *et al.*, in 2014 evaluated the effects of oral tramadol and placebo on the severity of postoperative shivering in patients with general anesthesia. The results showed that there was no significant difference between case and control groups in terms of shivering which was not consistent with our study. The type of surgery and sex difference of the patients can justify this inconsistency.<sup>[25]</sup> It seems that the use of alpha-2 agonists to prevent and reduce shivering in patients underwent spinal anesthesia is reasonable and appropriate. These drugs can have a sedative effect on the patients during surgery which lead to reduce anxiety. In our study, we could evaluate and compare other parameters such as sedation and postoperative analgesia.

## Conclusions

The use of methadone or alpha-2 agonists in patients with contraindications for meperidine is important. According to the results of the current study further studies are needed to confirm the effects of methadone and TI on shivering treatment, especially the dose and long-term side effects of medications. Moreover, it is proposed that injectable drugs including dexmedetomidine and methadone are used and compared for controlling and treating shivering.

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## Conflicts of interest

There are no conflicts of interest.

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