

# Reduction in the incidence of shivering with perioperative dexmedetomidine: A randomized prospective study

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## Abstract

**Background and Aims:** Shivering is distressing to the patient and discomforting to the attending anesthesiologist, with a varying degree of success. Various drugs and regimens have been employed to abolish the occurrence of shivering. The present study aims to explore the effectiveness of dexmedetomidine in suppressing the postanesthetic shivering in patients undergoing general anesthesia.

**Materials and Methods:** The present study was carried out on 80 patients, in American Society of Anesthesiologists I and II, aged 22–59 years, who underwent general anesthesia for laparoscopic surgical procedures. Patients were allocated randomly into two groups: group N ( $n = 40$ ) and group D ( $n = 40$ ). Group D were administered  $1 \mu\text{g}/\text{kg}$  of dexmedetomidine intravenously, while group N received similar volume of saline during peri-op period. Cardiorespiratory parameters were observed and recorded during the preop, intraop, and postop periods. Any incidence of postop shivering was observed and recorded as per 4 point scale. Side effects were also observed, recorded, and treated symptomatically. Statistical analysis was carried out using statistical package for social sciences (SPSS) version 15.0 for windows and employing ANOVA and chi-square test with post-hoc comparisons with Bonferroni's correction.

**Results:** The two groups were comparable regarding demographic profile ( $P > 0.05$ ). Incidence of shivering in group N was 42.5%, which was statistically highly significant ( $P = 0.014$ ). Heart rate and mean arterial pressure also showed significant variation clinically and statistically in group D patients during the postop period ( $P = 0.008$  and  $0.012$ ). A high incidence of sedation ( $P = 0.000$ ) and dry mouth ( $P = 0.000$ ) was observed in group D, whereas the incidence of nausea and vomiting was higher in group N ( $P = 0.011$  and  $0.034$ ).

**Conclusions:** Dexmedetomidine seems to possess antishivering properties and was found to reduce the occurrence of shivering in patients undergoing general anesthesia.

**Key words:** Dexmedetomidine, hypothermia, shivering, tramadol

## Introduction

Shivering is a protective mechanism by virtue of which heat production occurs, by vigorous involuntary muscle activity, to compensate for the decreased core temperature in a normal healthy living body. At molecular level, the reflex protective mechanism against cold gets kick started on perception of

lower temperature by the preoptic nucleus of hypothalamus.<sup>[1]</sup> The neurological mechanism of shivering is mediated by the spinal  $\alpha$ -motor neurons and their axons.<sup>[2]</sup>

Shivering is commonly encountered both after regional and general anesthesia (GA) with a little higher incidence in patients receiving GA.<sup>[3]</sup> It is distressing and uncomfortable and is perceived by many as equivalent to the postop surgical pain. It can hamper the normal smooth recovery and can be quite detrimental in certain group of patients, e.g., patients with raised intraocular pressure, raised intracranial tension, and with limited cardiorespiratory reserves such as elderly patients.<sup>[4,5]</sup> Excessive shivering creates an imbalance between body's oxygen demand and supply ratio. The resultant increased demand, sometimes up to six times than normal, and relative deficit of oxygen supply can lead to various metabolic derangements such as hypoxemia, lactic acidosis, and hypercarbia, thereby hampering a smooth recovery from anesthesia.<sup>[3]</sup>

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Various drugs, techniques, and measures have been used in the past to prevent incidence of shivering but the search for an ideal drug or drug combination is still on.<sup>[3,6,7]</sup> The desired properties for a drug to prevent shivering include easy availability and minimal side effects. Dexmedetomidine seems to have great potential for its usage in anesthesia and intensive care practice. It has been successfully used as adjunct to local anesthetics in neuraxial anesthesia and peripheral nerve blockade, as sedative agent during surgery and in ICU, as well as supplementation of postoperative analgesia.<sup>[8-12]</sup> It is also postulated that dexmedetomidine exhibits antishivering effects through its centrally mediated actions.<sup>[13,14]</sup> We had tried to find out the effectiveness of dexmedetomidine in prevention of postoperative shivering in patients who underwent GA for laparoscopic surgical procedures.

## Materials and Methods

After the approval from the hospital ethics committee, a prospective double blind randomized study was performed in our institute after obtaining a written informed consent from 80 ASA I and II patients of both genders aged 22–59 years. Patient with heart diseases, respiratory insufficiency, diabetes mellitus, psychiatric disorders, neuromuscular disorders, history of convulsions, thyroid disorders, multiple allergies, and patients with preoperative temperature  $>38^{\circ}\text{C}$  or  $<36.5^{\circ}\text{C}$  were excluded from the study.

The patients were randomly allocated by computer coded envelopes into two groups D and N of 40 patients each. Group D patients were administered a diluted solution of 2 ml of normal saline containing  $1\mu\text{g}/\text{kg}$  of dexmedetomidine, while group N patients were given a 2 ml of normal saline solution 30 minutes before the anticipated completion of surgery over 10 minutes. The treatment drugs were prepared by an anesthesia technician who was given a written set of instructions and was totally unaware of the study design. All the patients were premedicated with alprazolam 0.25 mg and ranitidine 150 mg orally with a sip of water a night before surgery and 2 hours before the proposed surgical procedure.

In the preop room, all the vitals including axillary temperature were observed and recorded into the performa by a staff nurse. In the operation theatre, all the baseline parameters such as heart rate (HR), electrocardiography (ECG), noninvasive blood pressure (NIBP), pulse oximetry ( $\text{SpO}_2$ ), and end tidal carbon dioxide ( $\text{EtCO}_2$ ) were recorded and an intravenous (IV) access was secured with an 18G cannula. Anesthetic management was standardized. Anesthesia was induced with propofol (2 mg/kg), fentanyl (1.5 mcg/kg), midazolam (1 mg), and vecuronium (0.1 mg/kg). Endotracheal intubation

was achieved with an appropriate-sized endotracheal tube. Axillary temperature was measured again after induction of anesthesia and thereafter every 20 minutes and also just before the administration of study drugs. All the patients were provided adequate covering of the body and operation room temperature was maintained at  $24\text{--}25^{\circ}\text{C}$ . Anesthesia was maintained with 60% nitrous oxide in oxygen, isoflurane 1–1.5% and vecuronium bromide 0.03–0.05 mg/kg as and when required. Palonosetron was also administered in a dose of  $75\mu\text{g}$  IV to all patients of both the groups 20–25 minutes before the anticipated completion of the surgical procedure. Neostigmine 2.5 mg and glycopyrrolate 0.5 mg was given to antagonize any residual neuromuscular blockade. Trachea was extubated after establishing the adequate return of protective airway reflexes and rhythmic breathing pattern with adequate tidal volume. All the vital parameters were duly observed and recorded into the performa.

In the recovery room, all the patients were covered with a warm blanket and were administered oxygen @ 3 L/min in a slightly propped-up position. Any episode of shivering, fever, pain, hallucination, dry mouth, postoperative nausea, and vomiting (PONV) and other complications were recorded by a Senior Anesthesia resident. Vital parameters HR, NIBP, ECG, and  $\text{SpO}_2$  were recorded at intervals of 5, 10, 20, 30, 45, and 60 minutes and half hourly thereafter for next 2 hours. Patients with any episode of PONV were treated with ondansetron 4 mg IV. Shivering was measured as per 4 point scale and any episode of shivering, of grade  $\geq 2$ , was treated with IV tramadol in a rescue dose of 25 mg [Table 1]. Sedation was graded as: 0 = no sedation/widely awake/slightly restless, 1 = calm and compose, 2 = opening eyes on verbal command, 3 = opening eyes on gentle shaking, 4 = opening eyes on vigorous shaking, and 5 = unarousable.

Statistical analyses were performed using statistical package for social sciences (SPSS) version 15.0 for windows. Mean differences between the two groups regarding age, weight, and height were calculated using analysis of variance (ANOVA). The chi-square test was used to analyze the difference between the gender, ASA class, the number of patients who developed shivering, and the number of patients who had other complications. Value of  $P < 0.05$  was considered as significant and  $P < 0.01$  as highly significant. Post-hoc

**Table 1: Grades of shivering**

Shivering grade	Clinical characteristics of shivering
1	No shivering
2	A small face or neck twitch muscle bundles, free arm movement without ECG interference
3	More than one muscle with trembling twitch
4	Gross muscular jitter of entire body

comparisons were performed using the Bonferroni's correction of the significance levels. Power analysis was carried out and for a detection of difference in the number of shivering patients; a sample size of 34 was calculated to achieve a power of 87% in the chi-square test with a significance level of 0.01 at group proportions of 0.6 and 0.1.

## Results

Both the groups were comparable regarding distribution of age, weight, height, gender, ASA grade, duration of anesthesia, and duration of surgery and were nonsignificant on statistical comparison [Table 2]. Patients administered dexmedetomidine had a more stable hemodynamic course during extubation and the recovery period. The pre-op mean HR and MAP were comparable in both the groups and did not reveal any statistical significance ( $P > 0.05$ ). Postoperatively, however, there was significant difference between the two groups as group D patients had a lower mean HR and MAP as compared to group N patients. HR and NIBP fluctuations were minimal in the group D as compared to group N during the period ranging from extubation to recovery in the postanesthesia care unit (PACU). These clinical parameters revealed a significant difference on statistical analysis [Table 3]. The other vital parameters such as respiratory rate, SpO<sub>2</sub>, EtCO<sub>2</sub>, general consciousness level, and alertness were almost similar in both the groups ( $P > 0.05$ ). However, sedation scores were observed to be higher in group D patients as 45% of the patients had a sedation score of 2 or higher measured on a subjective scale [Table 5].

The preoperative axillary temperature in both the groups was very much comparable (36.8°C in group D and 36.9 °C in

group N) and not significant during statistical comparison. Perioperatively, no major differences were observed between the two groups on repeated measurement of the temperature. Similarly, the average axillary temperature during the first 30 minutes in the postoperative period was measured to be 36.2 °C in the group N as compared to 36.4 °C in group D [Figure 1]. On statistical comparison, the difference in the axillary temperature between the two groups turned out to be nonsignificant ( $P > 0.05$ ).

There were 17 patients in the group N who had to be treated with rescue injection of tramadol for control of shivering in PACU as compared to just 2 patients in the D group. The demographic composition of the patients who had suffered from an episode of shivering in group N consisted of 7 females and 10 males with an average age of 36.84 ± 9.28 years and an average weight of 66.8 kg. Out of these 17 patients, 11 suffered grade 2 shivering, 4 reached grade 3, and only 2 had vigorous shivering of grade 4 in the first 1 hour of postoperative period. None of these patients

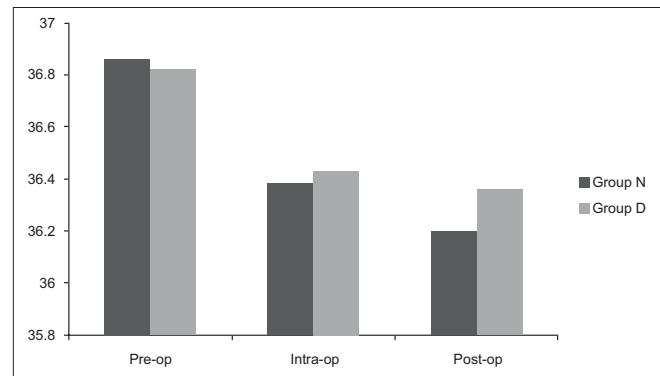


Figure 1: Response rate

Table 2: Demographic characteristics of Group N and Group D

Patient characteristic/Variable	Group N (n = 40)	Group D (n = 40)	P
Age (Mean ± SD)	38.42 ± 5.76	36.78 ± 6.68	0.72
Body weight (kg)	65.85 ± 7.26	68.12 ± 8.74	0.54
Height (cm)	164.28 ± 11.82	162.72 ± 10.46	0.62
American Society of Anesthesiologists grade I/II	27/13	30/10	0.33
Gender distribution (M/F)	17/23	14/26	0.21
Mean duration of surgery (in minutes)	57.86 ± 5.68	59.14 ± 4.28	0.78
Mean duration of anesthesia (in minutes)	64.42 ± 3.36	67.26 ± 4.12	0.52

Table 3: Comparisons of vital parameters in both the groups

Vital parameters	Group N (n = 40)	Group D (n = 40)	P
Mean heart rate (HR) (pre-op)	74.36 ± 8.22	73.54 ± 7.86	0.74
HR (post-op)	78.56 ± 6.64	65.28 ± 4.92*	0.008
Mean arterial pressure (MAP) (pre-op)	95.72 ± 9.44	92.48 ± 8.36	0.28
Mean arterial pressure (MAP) (post-op)	87.52 ± 8.18	77.28 ± 5.64*	0.012
Mean oxygen saturation (SpO <sub>2</sub> ) (pre-op)	98.18 ± 1.36	98.06 ± 1.28	0.86
SpO <sub>2</sub> (post-op)	98.81 ± 0.74	98.54 ± 0.65	0.77

\* $P < 0.05$ -Significant; \*\* $P < 0.01$ -Highly Significant

suffered any second attack of shivering after the injection of tramadol during the recovery period. The most striking statistics during recovery period pertained to the absence of any shivering in 95% of the patients who were administered intra-op dexmedetomidine as compared to only 57.5% of the patients in group N ( $P = 0.002$ ). The comparison of shivering statistics revealed a significant to highly significant difference on comparison between the patients of both the groups. [Table 4]

During the corresponding period, the pain scores were comparable on VAS scale and none of the patient in either of the group complained of any major pain episode except for mild discomfort which was very much tolerable. Four patients in the group N had episode of vomiting and a total of 7 patients suffered from nausea including these four as compared to just 1 and 2 patients in group D who suffered from similar episodes of PONV. This comparison was significant on statistical analysis ( $P < 0.05$ ). Dryness of oral mucosa is an established side effect of  $\alpha$ -2 agonists and the incidence was observed in 35% of the patients who were administered dexmedetomidine as compared to only 5% patients in the control group. The statistical comparison of the incidence of dry mouth turned out to be highly significant among the two groups ( $P = 0.000$ ) [Table 5].

## Discussion

Post-op shivering is as distressing to the patient as is pain and PONV though more stress is laid on the prevention of

**Table 4: Comparative incidence of grade of shivering in both the groups**

Shivering grade	Group N (n = 40) (%)	Group D (n = 40) (%)	P
1	23 (57.5)	38* (95)	0.002
2	11* (27.5)	2 (5)	0.014
3	4 (10)	0	-
4	2 (5)	0	-

\* $P < 0.05$ -Significant; \*\* $P < 0.01$ -Highly Significant

**Table 5: Comparison of side effect profile of both the groups**

Side effects	Group N (n = 40) No. of patients (%)	Group D (n = 40) No. of patients (%)	P
Headache	5* (12.5)	2 (5)	0.029
Nausea	7* (17.5)	2 (5)	0.011
Vomiting	4 (10)*	1 (2.5)	0.034
Dry mouth	2 (5)	13 (32.5)**	0.000
Myalgia	2 (5)	0	-
Sedation	4 (10)	18* (45)	0.000

\* $P < 0.05$ -Significant; \*\* $P < 0.01$ -Highly Significant

post-op pain and PONV. Its incidence is estimated to be as high as 50–60% in normal population undergoing GA.<sup>[4,15-17]</sup> The events like post-op shivering are often neglected and no universal protocols are established for its prevention. Though numerous research articles have laid emphasis on various pharmacological methods of prevention of shivering but nothing concrete has been incorporated into routine practice to prevent its occurrence.

The comparability of the demographic factors such as age, weight, height, gender distribution, duration of anesthesia, and surgery in the present study has ruled out any visible or confounding bias which could have affected the results of the study. Physical factors such as operating room temperature (24–25 °C), temperature of the recovery room, and temperature of the infused fluids are considered potential risk factors of shivering,<sup>[18]</sup> but these factors were very well controlled in the present study.

Thermoregulatory mechanisms get impaired during GA. As a result, hypothermia is one of the commonest complications during GA.<sup>[19-21]</sup> Though, shivering is a protective mechanism to preserve body heat but no definite linear relationship exists between body temperature and occurrence of shivering.<sup>[22]</sup> In the present study, nasopharyngeal temperature correlated well with the axillary temperature after applying a correction factor. A higher incidence of shivering in the control group defies the logic of hypothermia associated shivering as the mean differences of temperature in both the groups was comparable and statistically nonsignificant during the post-op period. These observations suggest that there must be some other factors also influencing the shivering mechanism and not just the presence of hypothermia alone.

Alpha-2 adrenergic agonists are widely used nowadays in clinical practice of anesthesiology and intensive care. Antishivering mechanism of dexmedetomidine has been studied but not adequately. In the present study, we obtained satisfactory results in the prevention of shivering in patients who were administered with dexmedetomidine as only 2 patients out of total 40 suffered an episode of shivering. The  $\alpha$ -2 receptor agonists are known to prevent shivering to a moderate extent without any associated respiratory depression as with other antishivering drugs like meperidine.<sup>[13,23]</sup> Dexmedetomidine reduces shivering by lowering vasoconstriction and shivering thresholds.<sup>[13,24]</sup> The findings of the present study provide an indirect support to the fact that antishivering action of dexmedetomidine is mediated by its central  $\alpha$ -2 activity.<sup>[25]</sup> The clinically significant effect at this dose includes mild sedation post-operatively which did not have any apparent effect on the ventilatory drive.<sup>[13,26]</sup> The difference in sedation scores between the two groups was statistically significant,

but the mild sedation induced by dexmedetomidine did not produce any other clinical side effect.

Alpha-2 adrenergic agonists decrease the central thermo sensitivity by suppressing the neuronal conductance.<sup>[27]</sup> This is mediated by the increased potassium conductance through Gi-coupled proteins which causes hyper polarization of neurons.<sup>[28-31]</sup> Augmentation of neural suppression response is further mediated by restriction of calcium entry into nerve cells which causes inhibition of neurotransmitter release.<sup>[31,32]</sup> The increased accumulation of calcium ions on the neuron's surface in the posterior hypothalamus lowers the firing rate of heat gain units by stabilizing the cell membrane.<sup>[33]</sup>  $\alpha$ -2 adrenergic agonists suppress the spontaneous firing rate of neurons in the locus coeruleus and neurotransmitter mediated firing of neurons in the dorsal raphe nucleus when administered intravenously.<sup>[34]</sup> All these central actions of  $\alpha$ -2 agonists are possible due to a high density of  $\alpha$ -2 adrenoceptors in the hypothalamus and activation of these receptors produces hypothermia by reduction of heat generated by metabolic activity.<sup>[14]</sup>

The incidence of shivering was 42.5% ( $n = 17$ ) in the control group as compared to a merely 5% in the study group. The incidence of shivering in the control group is relatively lower than that of observed incidence in other studies.<sup>[4,15,16,35]</sup> This may be due to the use of 75  $\mu$ g of 5HT3 antagonist palonosetron for the prophylaxis of PONV. These 5HT3 antagonists are being regularly used to prevent incidence of PONV in laparoscopic surgeries.<sup>[36]</sup> They have been used with moderate success in prevention of postoperative shivering as well as they can influence both metabolic heat production and heat loss pathways.<sup>[4,18,37]</sup>

The occurrence of dry mouth is an established fact with  $\alpha$ -2 adrenergic agonist and the incidence of 35% was observed in the present study. Patients had to be administered 5–10 ml of distilled water to wet the lips to overcome this discomforting side effect. Till date, there is no prophylactic treatment to counter this side effect as far as our knowledge is concerned.

Pethidine is considered the most effective antishivering drug in a dose of 25 mg.<sup>[38, 39]</sup> We however, preferred tramadol in a dose of 25 mg as rescue drug to control post-op shivering as the latter is not associated with respiratory depression.<sup>[40,41]</sup> Tramadol exerts its antishivering mechanism by inhibiting the reuptake of 5HT, nor-epinephrine, and dopamine and at the same time facilitating the release of 5HT.<sup>[42-44]</sup>

Limitations of the present study include the short duration of surgery as the mean duration of surgical period was calculated to be approximately 1 hour in both the groups. The antishivering

effect of dexmedetomidine needs to be seen in surgeries of longer duration where chances of developing hypothermia are more. We did not measure tympanic membrane temperature to measure the core temperature but applied a correction factor to the measured axillary temperature.

We conclude that dexmedetomidine seems to possess anti-shivering properties in a dose of 1  $\mu$ g/kg. Though few of the side effects such as sedation and dry mouth with dexmedetomidine are discomforting to the patient but they did not have any major clinical impact on the overall recovery from anesthesia.

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