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## Effects of Oral Clonidine in Preventing Postoperative Shivering After General Anesthesia

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**Abstract:** This randomized controlled study was performed to evaluate the efficacy of oral clonidine; an  $\alpha$  2-agonists which augments the inhibiting control of preoptic anterior hypothalamic region on the shivering center, before operation compared with placebo, in preventing postoperative shivering. Eighty ASA I and II patients, undergoing elective abdominal surgery under general anesthesia were randomized into two equal groups. Thirty minutes before anesthesia, patients were given either 0.2 mg oral clonidine (study group, n = 40) or placebo (control group, n = 40) as premedication. Patients were anesthetized with the same technique and drugs. Demographic and perioperative data, the incidence and severity of shivering were recorded in the recovery room. Data were analyzed to evaluate the effects of clonidine on the incidence and severity of postoperative shivering. Demographic and perioperative data were not significantly different between the two groups but emergence time was longer in clonidine group (p = 0.04). The incidence of postoperative shivering was 32.5% (13/40) in clonidine and 70% (28/40) in placebo group. The severity of shivering was significantly less frequent in the clonidine compared with placebo group (p<0.001). Oral clonidine in dose of 0.2 mg as premedication 30 min before surgery, reduced the incidence and severity of postoperative shivering but increased emergence time.

**Key words:** Shivering, clonidine, postoperative, general anesthesia

### INTRODUCTION

The incidence of postoperative shivering ranges between 6.3 and 66% (Alfonsi, 2001). This may be normal thermoregulatory shivering in response to core hypothermia during anesthesia or may result from the release of cytokines by the surgical procedure.

Postoperative shivering is very unpleasant and physiologically stressful. It may also cause complications, especially in patients with coronary artery disease, because of associated increases in oxygen consumption (by 100-600%), cardiac output, carbon dioxide production and circulating catecholamines and a significant decrease in mixed venous oxygen saturation. Moreover, an increase in intracranial and intraocular pressure, interference with monitoring of ECG and blood pressure, increased metabolic rate and lactic acidosis have been described in shivering patients (Mathew *et al.*, 2002; Dal *et al.*, 2005).

Postoperative shivering can be treated to maintaining normothermia by perioperative active warming and pharmacological treatment (Frank *et al.*, 1997; Piper *et al.*, 1999; Bilotta *et al.*, 2001, 2002).

The use of drugs is a common treatment of shivering including: pethidine, ketanserin, sufentanil, alfentanil, tramadol, physostigmine, urapidil, nefopam,

doxapram, nalbuphine and clonidine that are commonly used intravenously (Terasako and Yamamoto, 2000; Mathews *et al.*, 2002; De Witte and Sessler, 2002; Krankle *et al.*, 2002).

The shivering centre is under the inhibiting control of the preoptic anterior hypothalamic region. This control is strengthened by  $\alpha$  2-agonists. The aim of this study was to evaluate the effects of oral clonidine, an  $\alpha$  2-agonists as premedication, on the severity and incidence of postoperative shivering after general anesthesia.

### MATERIALS AND METHODS

This randomized, double-blinded clinical trial was performed in Dr. Shariati Hospital of Tehran University of Medical Sciences in 2006. The study protocol conformed to the ethical guidelines of the 1989 declaration of Helsinki and was approved by the investigational review board of Dr. Shariati Hospital.

Eighty ASA physical status I or II patients more than 18 years old, who were scheduled for elective abdominal surgery under general anesthesia, were studied and written informed consent was obtained from all subjects.

Exclusion criteria included anemia (Hb<9.0 g dL<sup>-1</sup>), respiratory, cardiac, hepatic and renal insufficiency, febrile

patients (>37.58°C), patients taking α 2-receptor agonists and pregnancy. No patient had a history of neuromuscular disease.

The patients were randomly assigned to receive either 0.2 mg oral clonidine (Tab 0.2 mg, Tolid-Daru™, IRAN) (C group, n = 40) or placebo (P group, n = 40) 30 min before surgery. Randomization was based on computer-generated codes that were concealed until interactions were assigned.

Drugs were given by an independent anesthetist in the ward, therefore both the anesthesiologist and the patient was blinded to the group assignment. On arrival in the operating room, ECG electrodes and Non Invasive Blood Pressure (NIBP) monitor were applied and oxygen saturation was monitored by pulse oxymeter.

Patients were anesthetized with the same technique including fentanyl 3 µg kg<sup>-1</sup> (Amp 10 mL, Fentanyl-Janssen™, Belgium), thiopentone 5 mg kg<sup>-1</sup> (Vial 1 g, Biochemie GmbH, Kundl-Austria) and atracurium 0.5 mg kg<sup>-1</sup> (Amp 10 mg mL<sup>-1</sup> Mayne Pharma Plc™, UK) to facilitate orotracheal intubation. General anaesthesia was maintained with isoflurane (0.4-1.6%) and 50% nitrous oxide in oxygen. Isoflurane was adjusted to the patient's requirements and to keep the mean arterial blood pressure (MAP) and Heart Rate (HR) within 20% of baseline values. Patients were not actively warmed during surgery and intravenous fluids were not administered through a warming device. Demographic data, duration of anesthesia, emergence time, nasopharyngeal temperature after the induction (T<sub>0</sub>) and at the end of anesthesia (T<sub>e</sub>) and time in the recovery room were recorded. The prophylactic effect on shivering was assessed and recorded by one of the investigators in charge of the postanesthesia care unit, who was not aware of the administered drug. Post anesthetic shivering was classified according to the five-point scale of Wrench *et al.* (1997) (Table 1).

**Statistical analysis:** A sample size of 40 patients in each group will be sufficient to detect a difference of 25% in shivering between the study groups assuming power of 85% and a significant level of 0.05. Statistical analysis was performed With SPSS package version 11.5. Data were analyzed by independent sample t-test, chi-square or fisher exact test when appropriate. p<0.05 was considered statistically significant.

Table 1: Shivering grade: 5-point scale modified by Wrench *et al.* (1997)

Grade 0	No shivering
Grade 1	One or more of: piloerection; peripheral vasoconstriction; peripheral cyanosis without other cause, but without visible muscular activity
Grade 2	Visible muscular activity confined to one muscle group
Grade 3	Visible muscular activity in more than one muscle group
Grade 4	Gross muscular activity involving entire body

## RESULTS AND DISCUSSION

Demographic data, duration of anesthesia, nasopharyngeal temperatures (T<sub>0</sub> and T<sub>e</sub>) and time in recovery room were not significantly different between the two groups but emergence time was longer in clonidine group (p = 0.04) (Table 2) (independent sample t-test and Chi-square).

Arterial blood pressure, heart rate and peripheral oxygen saturation remained stable during the operation. The incidence of postanesthetic shivering was 32.5% (13/40) in clonidine and 70% (28/40) in placebo group. The Severity of shivering, by using a scale similar to that validated by Wrench *et al.* (1997) was significantly less frequent in the clonidine group compared with the patients who received placebo (p<0.001, Fisher's exact test) (Fig. 1).

This study showed that oral clonidine as premedication, reduced the incidence and severity of postanesthetic shivering after general anesthesia.

Some risk factors for postoperative shivering that evaluated by sessler and review article by Alfonsi including: gender (male more than women), younger

Table 2: Demographic and perioperative data in study groups

Parameters	Clonidine (n = 40)	Placebo (n=40)
Sex (M/F)	19.0/21	25.0/15
Age (years)*	37.6±9.7	35.7±10.7
ASA (I/II)	26.0/14	24.0/16
Weight (kg)*	68.7±8.3	66.8±7.4
NT <sub>0</sub> (°C)*	36.1±0.3	36.2±0.4
NT <sub>e</sub> (°C)*	35.9±0.4	35.6±0.6
Duration of anesthesia (min)*	125.8±27.5	124.8±28.6
Emergence time (min)*	14.5±5.3 <sup>††</sup>	8.8±6.4
Time in the recovery room (min)*	48.5±13.4	41.2±14.6

NT<sub>0</sub> = nasopharyngeal temperature after induction of anesthesia; NTe = nasopharyngeal temperature at the end of anesthesia; \*: Data are presented as mean±SD; <sup>††</sup>: p<0.05 versus placebo

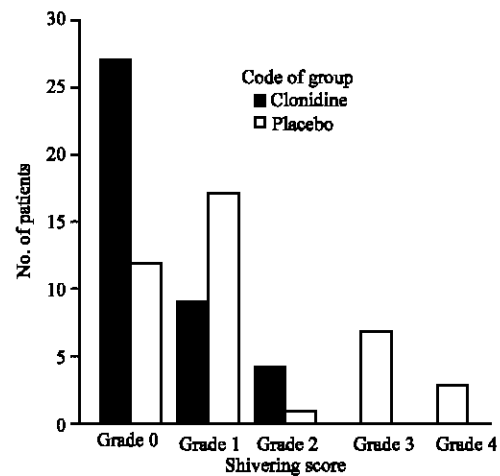


Fig. 1: Comparing the severity of postoperative shivering in the study groups

patients, length of the anesthesia or surgery (the longer the more likely), if no active perioperative rewarming procedure is used, drop in body temperature and type of anesthetic used (more with halogenated agents) (Sessler, 2000; Alfonsi, 2001).

In present study, the incidence of shivering in clonidine group was less than placebo group, 32.5% (13/40) vs 70% (28/40), respectively that was correlated with various study (Piper *et al.*, 2000; Kranke *et al.*, 2002; Stapelfeldt *et al.*, 2005).

Piper *et al.* (2000) performed a placebo-controlled study to evaluate the efficacy of urapidil compared with clonidine, meperidine and placebo in preventing postanesthetic shivering. They found that severity and incidence of shivering was less in meperidine and clonidine group that was correlated with our study. In this study emergence time in the clonidine group (14.5±5.3 min) was longer than placebo group (8.8±6.4 min) due to sedative effect of clonidine, that was similar to Piper *et al.* (2000) study, but no patient required therapeutic intervention.

Stapelfeldt *et al.* (2005) evaluate the effects of clonidine in 48 patients undergoing surgery for intracranial lesions, on preventing postoperative shivering and recovery from anesthesia.

They administered clonidine intravenously, 1 h before the end of anesthesia and found that; It did not delay emergence from anesthesia that was not correlated with present study but reduced postoperative shivering. This difference may be due to their different method for maintenance of anesthesia (Stapelfeldt *et al.*, 2005).

Our limitations were, not measuring clonidine plasma concentrations and using only one clonidine dose as oral tablet in all patients (0.2 mg).

In conclusion, oral clonidine in dose of 0.2 mg as premedication 30 min before surgery, reduced the incidence and severity of postoperative shivering but increased emergence time.

Further study with different dose of clonidine and serum concentration measurement may be required to evaluate the effect of this drug on postoperative shivering especially after induced hypothermia during surgery.

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#### REFERENCES

Alfonsi, P., 2001. Postanaesthetic shivering epidemiology, pathophysiology and approaches to prevention and management. *Drugs*, 61: 2193-2205.

Bilotta, F., P. Pietropaoli, I. La Rosa, F. Spinelli and G. Rosa, 2001. Effects of shivering prevention on hemodynamic and metabolic demands in hypothermic post operative neurosurgical patients. *Anaesthesia*, 56: 514-519.

Bilotta, F., P. Pietropaoli and G. Rosa, 2002. Nefopam and tramadol for the prevention of shivering during neuraxial anesthesia. *Regional Anesth. Pain Med.*, 27: 380-384.

Dal, D., A. Kose, M. Honca, S.B. Akinci, E. Basgul and U. Aypar, 2005. Efficacy of prophylactic ketamine in preventing postoperative shivering. *Br. J. Anaesthesia*, 95: 189-192.

De Witte, J. and D.I. Sessler, 2002. Perioperative shivering: Physiology and pharmacology. *Anesthesiology*, 96: 467-484.

Frank, S.M., L.A. Fleisher and M.J. Breslow *et al.*, 1997. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: A randomized clinical trial. *J. Am. Med. Assoc.*, 277: 1127-1134.

Kranke, P., L.H. Eberhart, N. Roewe and M.R. Tramer, 2002. Pharmacological treatment of postoperative shivering: A quantitative systematic review of randomized controlled trials. *Anesth. Analg.*, 94: 453-460.

Mathews, S., A. Al Mulla, P.K. Varghese, K. Radim and S. Mumtaz, 2002. Postanesthetic shivering-a new look at tramadol. *Anaesthesia*, 57: 394-398.

Piper, S.N., S.W. Suttner, C.C. Schmidt, W.H. Maleck, B. Kumle and J. Boldt, 1999. Nefopam and clonidine in the prevention of postanaesthetic shivering. *Anaesthesia*, 54: 695-699.

Piper, S.N., W.H. Maleck, J. Boldt, S.W. Suttner, C.C. Schmidt and D.J.P.A. Reich, 2000. Comparison of urapidil, clonidine, meperidine and placebo in preventing postanesthetic shivering. *Anesth. Analg.*, 90: 954-957.

Sessler, D.I., 2000. Perioperative heat balance. *Anesthesiology*, 92: 578-596.

Stapelfeldt, C., E.P. Lobo, R. Brown and P.O. Talke, 2005. Intraoperative clonidine administration to neurosurgical patients. *Anesth. Analg.*, 100: 226-232.

Terasako, K. and M. Yamamoto, 2000. Comparison between pentazocine, pethidine and placebo in the treatment of post-anaesthetic shivering. *Acta Anaesth. Scand* 44: 311-312.

Wrench, I.J., G. Cavill, J.E.H. Ward and A.W.A. Crossley, 1997. Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering. *Br. J. Anaesth.*, 79: 541-542.