Egyptian Journal of Anaesthesia (2015) **31**, 221–226

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Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

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Research Article

Efficacy of preoperative hydrocortisone versus tramadol for attenuation of postoperative shivering after percutaneous nephrolithotripsy: A randomized controlled trial

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Received 15 February 2015; revised 26 March 2015; accepted 22 April 2015
Available online 23 May 2015

KEYWORDS

Hydrocortisone;
Tramadol;
Postoperative shivering;
Percutaneous nephrolithotripsy

Abstract *Background:* Percutaneous nephrolithotripsy is a technique used for the treatment of renal stones during which an irrigation fluid is used which may cause hypothermia and shivering if not prevented. The aim of this prospective randomized placebo controlled double blinded study was designed to evaluate the efficacy of preoperative hydrocortisone versus tramadol for attenuation of postoperative shivering after percutaneous nephrolithotripsy under general anesthesia
Method: 90 ASA I males and females patients aged 20–50 years, planned for percutaneous nephrolithotripsy under general anesthesia were randomly divided into three groups:
Group S (n = 30) received 10 ml normal saline IV before induction of general anesthesia
Group H (n = 30) received IV hydrocortisone 2 mg/kg before induction of general anesthesia
Group T (n = 30) received IV tramadol hydrochloride 1 mg/kg before induction of general anesthesia
The following parameters were recorded:
Core temperature, heart rate and mean arterial blood pressure before induction of anesthesia, then every 15 min after induction of anesthesia, and every 30 min in the PACU, shivering intensity in the first 2 h postoperative, the incidence of shivering, the number of patients required meperidine and side effects.
Results: The number of patients who had shivering was statistically significantly higher in S group (12) than in H group (8) and in T group (7) with no statistically significant differences between H and T groups.
Intraoperative heart rate, mean arterial blood pressure and side effects showed no statistically significant difference between the study groups.

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Peer review under responsibility of Egyptian Society of Anesthesiologists.

http://dx.doi.org/10.1016/j.egja.2015.04.004

Conclusion: Preoperative IV hydrocortisone and tramadol were effective in attenuation of postoperative shivering compared to placebo after percutaneous nephrolithotripsy without increasing the incidence of side effects.

1. Introduction

Body core temperature is important for the maintenance of normal physiology of the body, and intraoperative hypothermia causes postoperative shivering, coagulation disorders, and prolongation of drug duration [1].

General anesthesia facilitates redistribution of the temperature from the central tissues to the peripheral tissues [2] causing perioperative hypothermia which complicates a large percentage of surgeries [3].

Percutaneous nephrolithotripsy (PCNL) is a common technique for the treatment of renal stones [4], and the use of irrigation fluid during endoscopic surgeries at room temperature may lead to hypothermia and shivering [5].

Malhotra et al. reported that fluid absorption occurred in 78% of the PCNL, and this may lead to inadvertent intraoperative hypothermia [6] and postoperative shivering which increase oxygen consumption, blood pressure, and intracranial and intraocular pressures [7].

Many drugs such as meperidine, ondansetron and clonidine have been used for the prevention of shivering [8].

Hydrocortisone has been found to be effective in the prevention of postoperative shivering after general anesthesia [9].

Tramadol hydrochloride, a synthetic opioid, prevents shivering by inhibiting the reuptake of serotonine, dopamine and norepinephrine [10], and previous studies showed that tramadol is a potent prophylactic antishivering agent [11–13].

The aim of this prospective randomized placebo controlled double blinded study was to evaluate the efficacy of preoperative hydrocortisone versus tramadol for attenuation of postoperative shivering after percutaneous nephrolithotripsy under general anesthesia.

2. Patients and methods

After approval from the ethical committee in Faculty of medicine, Beni suef university hospital (FMBSU REC, Egypt), the study was registered at the Australian New Zealand Clinical Trials Registry (ANZCTR), the registration number is ACTRN12614000413628, and written informed consents were obtained from 90 ASA I male and female patients aged 20–50 years, who were planned for percutaneous nephrolithotripsy under general anesthesia from May 2014 to January 2015.

Patients were excluded from the study if they are ASA > I, had history of peptic ulcer, or are on prolonged steroid therapy, and those with history of use of antidepressant drugs, epilepsy, a known allergy to the study drugs, expected blood transfusion during surgery, BMI > 30 or an initial body temperature > 38 °C or < 36 °C were also excluded.

On arrival to the operating theater, 18 G intravenous cannula was inserted and IV warmed crystalloid fluid was infused.

The patients were randomly divided using closed envelope technique for randomization to one of three groups:

Group S (n = 30): received 10 ml normal saline IV.
Group H (n = 30): received IV hydrocortisone 2 mg/kg.
Group T (n = 30): received IV tramadol hydrochloride 1 mg/kg.

The studied drugs were diluted in 10 ml coded syringes and given as an IV bolus just before induction of general anesthesia by an anesthesiologist who is unaware of the study protocol.

With adjustment of the temperature in operating room at 22 °C –24 °C, the monitor was attached to the patients to take preoperative readings of heart rate, non-invasive arterial blood pressure, and SpO_2.

General anesthesia was induced after preoxygenation for 3–5 min with 100% oxygen by face mask, then anesthesia was induced in all patients with the use of IV fentanyl 2 μg/kg, IV propofol 1.5–2 mg/kg, and atracurium 0.5 mg/kg and they were ventilated manually with sevoflorane 2 volume%, 100% oxygen via a face mask and then oral cuffed endotracheal tube was inserted. Muscle relaxation was guided by nerve stimulator anesthesia was maintained with oxygen 100%, sevoflorane, additional doses of atracurium, and mechanical ventilation with maintenance of end tidal carbon dioxide 35–40 mmHg.

The patients were covered with sheets and sterile surgical drapes, and all intravenous fluids and irrigation fluids were warmed.

At the end of surgery, neuromuscular blockade was reversed with IV neostigmine 0.04 mg/kg and atropine 0.02 mg/kg, the trachea was extubated when the patient responds to commands, and all patients were transferred to PACU, where they received oxygen via face mask 3–4 l/min and were monitored and covered with cotton blanket.

The following parameters were recorded by senior anesthesia resident unaware of the study protocol:

1. Patient characteristics and operation time.
2. Core temperature (°C) (tympanic membrane temperature by Rossmax® medical infrared ear thermometer, radiant innovation Inc., Taiwan) before induction of anesthesia, then every 15 min after induction of anesthesia, and every 30 min in the PACU.
3. Shivering intensity in the first 2 h postoperative was graded by using a five-point scale that was used in the study of Honarmand and Safavi [8].

(Grade 0: none; Grade 1: one or more areas of Pilo erection but without visible muscular activity; Grade 2: visible muscular activity confined to one muscle group; Grade 3: same as Grade 2 but in more than one muscle group; and Grade 4: gross muscular activity involving the entire body). If grades 3 shivering was observed the patients were treated with IV meperidine 25 mg.

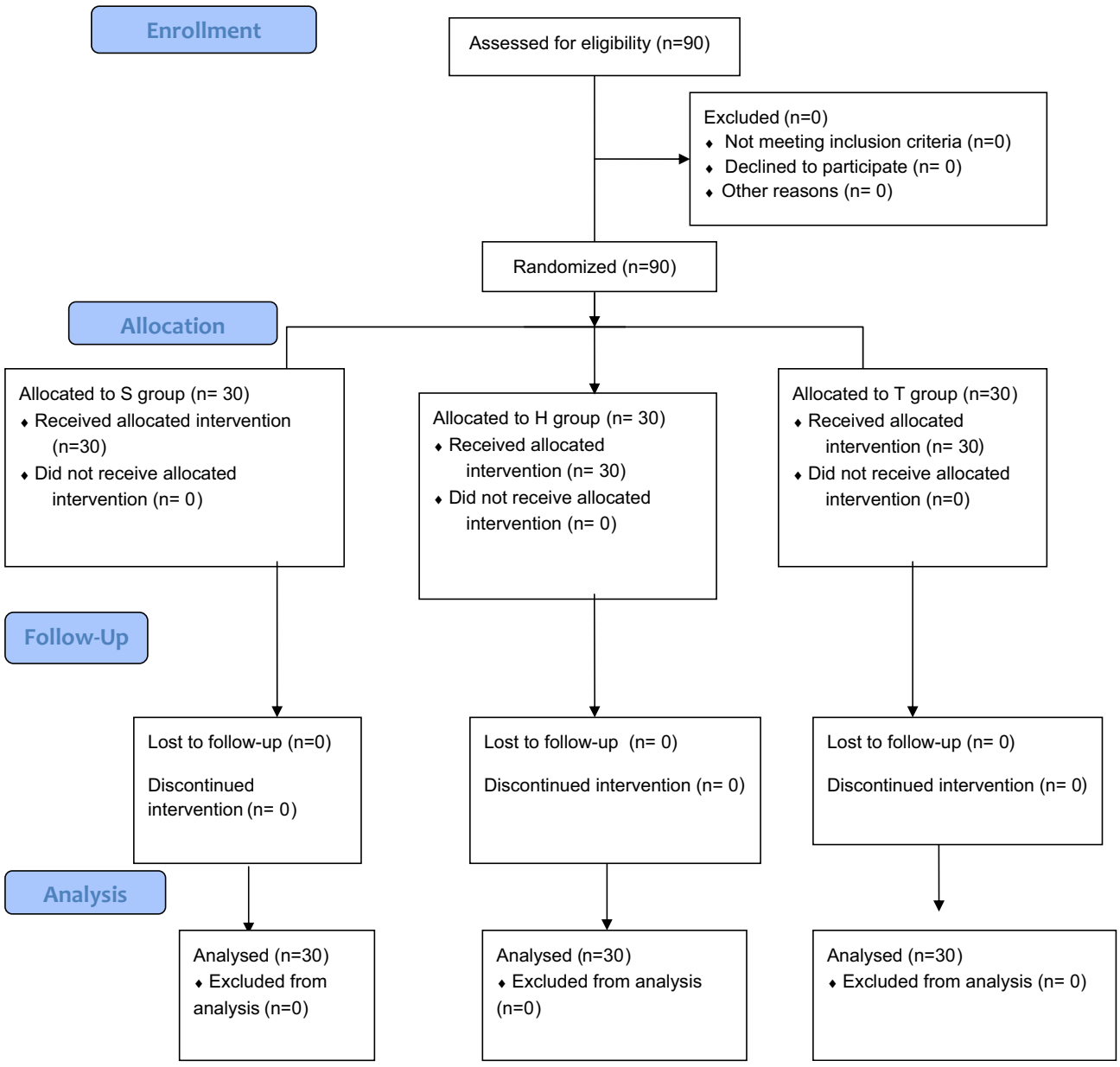

Figure 1 90 patients completed the study.

4. The incidence of shivering.
5. Number of patients requiring meperidine.
6. Heart rate and mean arterial blood pressure were recorded before anesthesia, every 15 min after anesthesia, and every 30 min in the recovery room.
7. Side effects:
   - Nausea and vomiting:
   - Hypotension (decrease in MAP > 20% from preoperative reading).
   - hypertension (increase in MAP > 20% from preoperative reading).
   - tachycardia (increase in HR > 20% from preoperative reading).

3. Statistical analysis

Data are presented as mean and standard deviation (SD) or median (range) or numbers as appropriate, and parametric data were analyzed using one way ANOVA. Nonparametric data were analyzed by using the Kruskal–Wallis test. P values <0.05 were considered statistically significant, and the significance of the differences in three sample means is being evaluated using F-test (ANOVA). The alpha level is $\alpha = 0.05$ and the power is 0.90 using G Power program. Statistical package for social science (SPSS) software version 15 was used.

4. Results

All patients completed the study, flow diagram Fig. 1.

Patient's characteristics and operative data showed no statistically significant difference between the studied groups, Table 1.

Core temperature showed no statistically significant difference between the study groups, Table 2.

Number of Patients developed shivering was statistically significantly higher in S group (12) than in H group (8) and T group (7) with no statistically significant difference between H and T groups.

Number of patients had grade 0 shivering was higher in groups H and T compared to group S with no statistically significant difference between the three groups, grade 3 shivering was higher in group compared to group H and group T, no patient had grade 4 shivering, and number of patients received meperidine was lower in groups H and T compared to group S. Table 3.

Intraoperative heart rate, mean arterial blood pressure and side effects showed no statistically significant differences between the study groups Tables 4–6.

Table 1 Demographic data, duration of operation. Data are presented as mean ± SD, numbers.

Variables	S (n = 30)	H (n = 30)	T (n = 30)
Age (year)	35.1 ± 8.92	32.66 ± 7.93	34.76 ± 10.41
Weight (kg)	83.93 ± 6.50	82.13 ± 8.32	84.53 ± 7.67
Height (cm)	165.2 ± 7.35	164.56 ± 7.52	164.2 ± 7.077
Sex (male/female)	19/11	18/12	20/10
Duration of operation (min)	101.83 ± 10.46	100 ± 10.82	101 ± 11.24

Group S: received 10 ml normal saline IV.
Group H: received IV hydrocortisone 2 mg/kg.
Group T: received IV tramadol hydrochloride 1 mg/kg
No statistically significant difference between the study groups, P value >0.05.

Table 2 Core temperature °C. Data are presented as mean ± SD.

	S (n = 30)	H (n = 30)	T (n = 30)
Temperature			
Preoperative	36.95 ± 0.15	36.93 ± 0.17	36.88 ± 0.21
15 min	36.72 ± 0.42	36.87 ± 0.31	36.88 ± 0.30
30 min	36.77 ± 0.39	36.66 ± 0.43	36.5 ± 0.48
45 min	36.69 ± 0.44	36.89 ± 0.27	36.87 ± 0.30
60 min	36.65 ± 0.45	36.79 ± 0.40	36.84 ± 0.34
75 min	36.66 ± 0.47	36.84 ± 0.35	36.85 ± 0.34
90 min	36.07 ± 0.44	36.44 ± 0.48	36.45 ± 0.49
105 min	35.86 ± 0.41	36.11 ± 0.39	36.39 ± 0.44
PACU			
0 min	35.95 ± 0.15	36.03 ± 0.17	36.0 ± 0.20
30 min	36.01 ± 0.42	36.87 ± 0.31	36.88 ± 0.30
60 min	36.65 ± 0.47	36.79 ± 0.37	36.83 ± 0.35
90 min	36.71 ± 0.42	36.8 ± 0.31	36.88 ± 0.30
120 min	36.81 ± 0.38	36.90 ± 0.26	36.92 ± 0.25

Group S: received 10 ml normal saline IV.
Group H: received IV hydrocortisone 2 mg/kg.
Group T: received IV tramadol hydrochloride 1 mg/kg.
No statistically significant difference between the study groups, P value >0.05.

Table 3 Incidence, severity of shivering and number of patients received meperidine. Data are presented as numbers (%).

Variables	S (n = 30)	H (n = 30)	T (n = 30)
Patients developed shivering no (%)	12 (40)*	8 (26.6)	7 (20)
Grades of shivering			
Grade 0	18	22	23
Grade 1	5	3	2
Grade 2	2	2	3
Grade 3	5	3	2
Grade 4	0	0	0
Patients received meperidine(n)	5	3	2

Group S: received 10 ml normal saline IV.
Group H: received IV hydrocortisone 2 mg/kg.
Group T: received IV tramadol hydrochloride 1 mg/kg.
No statistically significant difference between the study groups, P value >0.05.

5. Discussion

Postanesthetic shivering is common after general anesthesia with an incidence up to 60% [11], and it can cause rise in oxygen consumption and increase in intraocular and intracranial pressures[12].

Postanesthetic shivering may occur due to unintended intraoperative hypothermia which may be due to a cool operating room, infusion of cool fluids, and the effects of anesthetic drugs [14].

The results of the present study showed that preoperative IV hydrocortisone and tramadol were effective in attenuation of postoperative shivering compared to placebo after percutaneous nephrolithotripsy without increasing the incidence of side effects.

In the present study preoperative IV tramadol hydrochloride 1 mg/kg was effective in attenuation of postoperative shivering compared to placebo without increasing g the incidence of side effects.

The efficacy of tramadol in prevention of postoperative shivering was investigated in many studies using different doses and regimes.

Angral et al. [10] showed that IV tramadol 1 mg/kg given at the end of the operation was effective in reducing the incidence and severity of shivering after open and laparoscopic cholecystectomy compared to placebo without increasing the incidence of side effects.

Mathews et al. [11] concluded that intravenous tramadol 2 mg/kg and 1 mg/kg given at the time of wound closure were effective in prevention of postanesthetic shivering after general anesthesia compared to placebo without increasing the incidence of side effects as vomiting. In the high-dose group, 2%

Table 4 Heart rate (Bpm). Data are presented as mean ± SD.

Variable	S (n = 30)	H (n = 30)	T (n = 30)
Preinduction	78.9 ± 6.99	76.13 ± 6.90	77.06 ± 6.79
15 min	79.5 ± 7.79	76.46 ± 6.17	77.83 ± 6.59
30 min	74.86 ± 6.16	73.3 ± 7.92	74.3 ± 7.11
45 min	76.53 ± 4.59	74.96 ± 4.70	74.66 ± 5.61
60 min	72.8 ± 7.00	72.5 ± 5.13	71.8 ± 6.52
75 min	74.76 ± 4.65	72.83 ± 3.92	73 ± 4.07
90 min	75.23 ± 5.32	72.7 ± 4.91	72.9 ± 5.35
105 min	74.86 ± 4.53	73.2 ± 4.75	73.3 ± 4.88
PACU			
0 min	80.3 ± 7.52.	77.43 ± 6.27	78.46 ± 6.32
30 min	79.9 ± 7.43	76.96 ± 5.81	78.23 ± 6.33
60 min	80.2 ± 7.57	77.56 ± 5.78	78.5 ± 6.57
90 min	79.5 ± 7.61	76.86 ± 6.17	78.06 ± 6.38
120 min	74.53 ± 4.55	72.76 ± 6.59	72.63 ± 4.70

Group S: received 10 ml normal saline IV.
Group H: received IV hydrocortisone 2 mg/kg.
Group T: received IV tramadol hydrochloride 1 mg/kg.
No statistically significant difference between the study groups, P value >0.05.

Table 6 Side effects. Data are presented as numbers.

Variable	S (n = 30)	H (n = 30)	T (n = 30)
Nausea	2	1	3
Vomiting	0	0	1
Hypotension	0	0	0
Hypertension	0	0	0
Tachycardia	0	0	0

Group S: received 10 ml normal saline IV.
Group H: received IV hydrocortisone 2 mg/kg.
Group T: received IV tramadol hydrochloride 1 mg/kg.
No statistically significant difference between the study groups, P value >0.05.

of patients had postanesthetic shivering, compared to 4% in the low-dose group and 48% in the control group.

A study by Enakshi et al. [12] concluded that IV tramadol 1 mg/kg before wound closure was effective in prevention of postoperative shivering after open and laparoscopic cholecystectomy without increasing the side effects.

M. Mohta [13] used tramadol concentrations of 1, 2 and 3 mg/kg at the time of wound closure in patients who underwent elective abdominal operations under general anesthesia, which was an effective antishivering agent compared to pethidine 0.5 mg/kg.

Heidari et al. [15] reported that oral tramadol 50 mg as a premedication was effective in the prevention of postanesthetic shivering after general anesthesia, 5 patients (12.5%) had postanesthesic shivering in tramadol group and 10 patients (25%) had postanesthesic shivering in the placebo group. The incidence of grade III and grade IV shivering was 7.5% and 25% in tramadol and placebo groups, respectively.

Heid et al. [16] reported that compared with placebo, intraoperative intravenous administration of tramadol in a dose of 2 mg/kg 45–30 min before skin closure reduced the incidence and severity of postoperative shivering in patient undergoing lumbar disk surgery.

The incidence of shivering in tramadol group was 20% versus. 70% in placebo group, and severe shivering occurred in 10% in tramadol group versus 46.7% in placebo group. Tramadol inhibits the neuronal reuptake of norepinephrine and 5-hydroxytrytpamine, facilitates the release of 5-hydroxytrytpamine, and activates μ-opioid receptors, these effects may influence thermoregulatory control, and the attenuating effect of tramadol on shivering may be due to the additive or synergistic action of kappa opioid receptor and α2 adrenergic mechanisms [17].

Pawar et al. reported that hydrocortisone 1–2 mg/kg iv was effective in prevention of postoperative shivering after knee arthroscopy under general anesthesia [9].

Table 5 Mean arterial blood pressure. Data are presented as mean ± SD.

Variable	S (n = 30)	H (n = 30)	T (n = 30)
Preinduction	87.76 ± 6.97	89.56 ± 5.04	84.63 ± 6.84
15 min	76.4 ± 7.49	79.46 ± 6.34	77.73 ± 6.68
30 min	78.83 ± 9.74	80.3 ± 10.76	79 ± 9.68
45 min	80.5 ± 7.83	79.7 ± 11.32	82.13 ± 3.48
60 min	77.2 ± 5.95	78 ± 4.98	76.26 ± 4.61
75 min	78.96 ± 7.48	78.46 ± 6.03	77.33 ± 6.09
90 min	79.06 ± 6.35	78.83 ± 10.67	81.4 ± 7.51
105 min	82.2 ± 5.21	81.9 ± 12.35	79.5 ± 11.83
PACU			
0 min	83.96 ± 8.79	80.26 ± 10.07	84.2 ± 7.24
30 min	85.2 ± 7.40	83.53 ± 8.83	84.96 ± 6.93
60 min	85.46 ± 5.81	83.23 ± 8.48	84.23 ± 7.72
90 min	82.66 ± 6.06	81.56 ± 7.01	83.7 ± 5.79
120 min	82.8 ± 11.29	80.76 ± 10.45	84.2 ± 7.59

Group S: received 10 ml normal saline IV.
Group H: received IV hydrocortisone 2 mg/kg.
Group T: received IV tramadol hydrochloride 1 mg/kg.
No statistically significant difference between the study groups, P value >0.05.

Qioa et al. [18] showed that hydrocortisone 2 mg/kg iv was effective in treating shivering after spinal anesthesia in cesarean section.

The mechanism by which hydrocortisone prevents shivering is not known [9]. A previous animal study showed that glucocorticoids have an anabolic effect with an increase in the levels of hepatic ATP [19].

A study by Yared et al. [20] concluded that the incidence of shivering after cardiac surgery was reduced by dexamethasone due to modification of the inflammatory response and the reduction of the gradient between core and skin temperatures.

Murphy et al. [21] also concluded that the use of dexamethasone before induction of general anesthesia reduced the incidence of postoperative shivering in ICU in patients undergoing elective cardiac surgery.

Hosseinzadeh et al. [22] showed that administration of hydrocortisone and dexamethasone before induction of general anesthesia significantly decreases the rate and severity of postanesthesia shivering through anti inflammatory mechanisms and reduction of central and skin gradient by these drugs.

6. Conclusion

Preoperative hydrocortisone and tramadol were effective in attenuation of postoperative shivering compared to placebo after percutaneous nephrolithotripsy without increasing the incidence of side effects.

Conflict of interest

None.

References

[1] Kurz A. Physiology of thermoregulation. Best Pract Res Clin Anaesthesiol 2008;22(4):627–44.

[2] Alfonsi P. Postanesthetic shivering. Epidemiology, pathophysiology and approaches to prevention and management. Minerva Anestesiol 2003;69(5):438–42.

[3] Horosz Bartosz. Magorzata Malec-Milewska. Inadvertent intraoperative hypothermia. Anaesthesiol Intens Ther 2013;45(1):38–43.

[4] Mohta M, Bhagchandani T, Tyagi A, Pendse M, Sethi AK. Haemodynamic, electrolyte and metabolic changes during percutaneous nephrolithotomy. Int Urol Nephrol 2008;40(2):477–82.

[5] Yinghui Jin, Jinhui Tian, Mei Sun, Kehu Yang. A systematic review of randomized controlled trials of the effects of warmed irrigation fluid on core body temperature during endoscopic surgeries. J Clin Nurs 2011;20(3–4):305–16.

[6] Malhotra SK, Khaitan A, Goswami AK, Gill KD, Dutta A. Monitoring of irrigation fluid absorption during percutaneous nephrolithotripsy: the use of 1% ethanol as a marker. Anesthesia 2001;56(11):1090–115.

[7] Entezariasl M, Isazadehfar K. Dexamethasone for prevention of postoperative shivering: a randomized double-blind comparison with pethidine. Int J Prev Med 2013 Jul;4(7):818–24.

[8] Honarmand A, Safavi MR. Comparison of prophylactic use of midazolam, ketamine, and ketamine plus midazolam for prevention of shivering during regional anesthesia: a randomized double-blind placebo controlled trial. Br J Anaesth 2008;101(4):557–62.

[9] Pawar MS, Suri N, Kaul N, Lad S, Khan RM. Hydrocortisone reduces postoperative shivering following day care knee arthroscopy. Can J Anaesth 2011;58(10):924–8.

[10] Angral R, Wani AA, Kapoor BB. Tramadol and postoperative shivering in patients undergoing open and laparoscopic cholecystectomy under general anaesthesia. South Afr J Anaesth Analg 2012;18(2):111–4.

[11] Mathews S, Al Mulla A, Varghese PK, Radim K, Mumtaz S. Postanaesthetic shivering: a new look at tramadol. Anesthesia 2002;57(4):394–8.

[12] Enakshi S, Manjushree R, Gouri M. Effect of tramadol in prevention of postanesthetic shivering following general anesthesia for cholecystectomy. Indian J Anaesh 2005;49(3):208–12.

[13] Mohta M, Kumari N, Tyagi A, Sethi AK, Agarwal D, Singh M. Tramadol for prevention of postanesthetic shivering: a randomized double-blind comparison with pethidine. Anaesthesia 2009;64(2):141–6.

[14] Adriani Melissa Bucci, Moriber Nancy. Preoperative forced-air warming combined with intraoperative warming versus intraoperative warming alone in the prevention of hypothermia during gynecologic surgery. AANA J 2013;81(6):446–51.

[15] Heidari SM, Rahimi M, Soltani H, Hashemi SJ, Shabahang S. Premedication with oral tramadol reduces severity of postoperative shivering after general anesthesia. Adv Biomed Res 2014;27(3):64.

[16] Heid F, Grimm U, Roth W, Piepho T, Kerz T, Jage J. Intraoperative tramadol reduces shivering but not pain after remifentanil–isoflurane general anesthesia. A placebo-controlled, double-blind trial. Eur J Anaesthesiol 2008;25(6):468–72.

[17] Javaherforoosh F, Akhondzadeh R, Aein KB, Olapour A, Samimi M. Effects of Tramadol on shivering post spinal anesthesia in elective cesarean section. Pak J Med Sci 2009;25(1):12–7.

[18] Qioa W, Tang G, Cheng W, Zhou H, Su L, Pei M, Tang H. Effects of treatment with pethidine and hydrocortisone on postspinal anesthesia shivering in cesarean section. J Nantong Univ Med Sci 2010(05).

[19] Feigelson P, Feigelson M. Studies on the mechanism of regulation by cortisone of the metabolism of liver purine and ribonucleic acid. J Biol Chem 1963;238(3):1073–7.

[20] Yared Jean-Pierre, Starr Norman J, Hoffman-Hog Lori, Bashour C Allen, Insler Steven R, O'Connor Michael, et al. Cosgrove. Dexamethasone decreases the incidence of shivering after cardiac surgery: a randomized, double-blind, placebo-controlled study. Anesth Analg 1998;87(4):795–9.

[21] Murphy GS, Sherwani SS, Szokol JW, Avram MJ, Greenberg SB, Patel KM, Wade LD, Vaughn J, Gray J. Small-dose dexamethasone improves quality of recovery scores after elective cardiac surgery: a randomized, double-blind, placebo-controlled study. J Cardiothorac Vasc Anesth 2011;25(6):950–60.

[22] Hosseinzadeh H, Eydi M, Dadashzadeh S, Kolahdouzan KH, Pesyanian E. The effect of preoperative hydrocortisone on the rate and severity of post anesthesia shivering. J Pharmaceut Sci Fall 2005;3:33–7.