Original Article

The effect of intravenous infusion of paracetamol before anesthesia induction on the core and peripheral temperature changes and post-operative shivering in patients undergoing general anesthesia

Gholamreza Khalili, Parvin Sajedi, Azam Alinaghian

Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Post-operative shivering is an unpleasant complication that various drugs are used to prevent and treat. It is tried to advice a suitable drug with the least side-effects. This study was carried out to examine the effect of intravenous Apotel on the post-operative shivering and core and peripheral body temperature.

Materials and Methods: This clinical trial conducted in Al Zahra and Kashani Hospitals in Isfahan in 2012 on 64 patients undergoing upper limbs surgery with general anesthesia, which divided in two equal groups. In the first group, before induction, 15 mg/kg and up to 1 g paracetamol was infused in 100 cc normal saline within 20 min and control group was infused 100 cc normal saline during 20 min. Post-operative shivering and pain were recorded in the same time in addition to the core and peripheral temperature. The results were analyzed by SPSS ve.20 software.

Results: In patients receiving Apotel, the core and peripheral temperature were significantly lower ($P < 0.05$). At 10 min after entering in recovery, 10 patients in the control group and 2 in the intervention group suffered from shivering (31.2% vs. 6.2%), which was significantly different ($P = 0.02$). Nineteen patients (29.7%) suffered from shivering in recovery (14 patients in the control group and 5 patients in the intervention group (43.8% vs. 15.6%)). In Apotel receiving group, the incidence of shivering in recovery was significantly lower ($P = 0.014$).

Conclusion: Given the beneficial effects of Apotel in post-operative shivering and pain reduction, using the drug as a pre-drug is recommended in patients undergoing surgery with general anesthesia.

Key Words: Apotel, paracetamol, post-operative shivering

Address for correspondence:
Prof. Parvin Sajedi, School of Medicine, Department of Anesthesia, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: sajedi@med.mui.ac.ir
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INTRODUCTION

Hypothermia induced by anesthetics in general anesthesia. During surgery, the hypothermia pattern occurs as a rapid initial reduction of the core body temperature followed by a slow linear decline and eventually remains constant.[1]

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The mechanism of reducing the core body temperature by anesthetics, vasodilatation, is a reduction of metabolic rate to 20-30%. The core body temperature includes the temperature of the head, body and limbs is 2-4°C lower than the core body temperature that is due to the tonic Thermoregulatory vasoconstriction in the environment, but anesthesia destroys the vasoconstriction and causes to transfer the heat to the environment. After the initial redistribution, the reduction of core body temperature becomes slow and it linearly decreases for 2-4 h that is due to losing heat more than producing metabolic heat.[1] Finally, plateau, which is created 4-3 h after the anesthesia onset is obtained that caused peripheral thermoregulatory vasoconstriction, which has been stimulated by the temperature of 33-35°C.

Hypothermia with inhaled anesthetics is created more than intravenous anesthetic drugs and it has been recommended monitoring temperature in patients undergoing surgery over 30 min and trying to keep the temperature higher than 36°.[2]

Post-operative shivering differs between 5% and 65% depending upon the kind of general or regional anesthesia.[1] The hypothermia complication includes coagulation disorder, increasing bleeding, requirement to allogeneic transfusion to 20%, wound infection by stimulating vasoconstriction, tissue hypoxia, delayed wound healing, increasing the length of hospitalization to 20%, the risk of myocardial ischemia during surgery, reducing the drugs metabolism and increasing the recovery period through this reduction.[3]

Shivering complication includes an unpleasant feeling which can cause stress in patient, strain and pressure on the wound place and increase pain, body metabolism rate and as a result raises the oxygen consumption to 400% and sometimes up to 600% that leads to arterial hypoxemia raise in carbon dioxide production and lactic acidosis and increasing catecholamines in circulating blood. Increasing in intracranial and intraocular pressure and creating the artifact in monitoring are of its other complications.[4,5]

Nowadays, using intravenous paracetomol is increasing for post-operative analgesia and reduced opioid consumption.[6] Paracetamol is a non-steroidal anti-inflammatory drug that affects the core body temperature through affecting the hypothalamus (by affecting the prostaglandins synthesis in hyperthermia).[7,8] Therefore, using intravenous paracetamol for post-operative analgesia and reducing opioid consumption is increasing, it has been recommended that during surgery, the core temperature should be maintained over 36°.[9-11] The study was carried out to show the effect of intravenous paracetamol on core body temperature changes, the incidence and intensity of post-operative shivering in anesthesia during the recovery period and comparison with the control group.

MATERIALS AND METHODS

This double-blinded randomized clinical trial study was conducted in Al Zahra and Kashani Medical Centers, in Isfahan in 2012. The objective population consisted of patients with 18 to 70 years old and American Society of Anesthesiologists (ASA) I, II, under surgery by general anesthesia that took more than an hour and at most 2.5 h and those without renal or liver disease and lack of chronic use of acetaminophen, NSAID and opium drugs. Furthermore, patients needing a blood transfusion and receiving non-crystalloid fluids and having any sensitivity to paracetamol excluded from this study. Using the formula of estimating the sample size, the required sample size was determined (based of 5% alpha (1-Z1) and 20% beta (1-Z2) to compare two means with 32 individuals in each group of the patients were normotherm and have no fever with core temperature of 36.5 ± 0.8 and peripheral temperature of 36.9 ± 0.7. *T*-test showed that there was no difference in these factors (P = 0.013). The significant level was 0.05.

Patients with inclusion criteria were computerized randomly divided into two 32 populated groups that anesthesia technique and therapy fluid were similar in both groups. All patients have been kept NPO for 8 h and during this time, therapy fluid was performed according to 1, 2, 4 principle from 1.3 to 2.3 serums. Patients underwent routine monitoring. Before starting induction, during 20-min, patients in the intervention group were infused by 100 cc of normal saline with 1 g Paracetamol and patients in the control group were infused by 100 cc of normal saline and the peripheral temperature was measured before induction by the probe connected to monitoring in the operation room and the core temperature by tympanic thermometer. Then, the induction was conducted through 5-7 mg/kg sodium thiopental, 2 μg/kg Fentanyl and 0.6 mg/kg Atracurium and patients were intubated and the core and peripheral temperature were measured. Continuing anesthesia was done by 1-1.2% Isoflurane and 50%N2O and the core and peripheral temperature was taken every 10 min until ½ h and then every ½ h until the end of surgery during anesthesia. Atracurium was replicated if it was necessary. 0.1 mg/kg Morphine

was given to patients at the beginning of operation and the temperature of the operation room was maintained between 22°C to 26°C and fluids injecting in patients were Crystalloids of isothermal with environment. During the surgery, all patients were covered by a cloth layer over the chest and legs areas. At the end of the operation, the patient was reversed by 0.02 mg/kg atropine and 0.04 mg/kg neostigmine, covered by a layer of a cotton blanket and transferred to the recovery room. The temperature of the recovery room was the same for all patients and no heating device was separately used. If the core temperature reached below 36°, hypothermia has been considered and at the same time with measuring the core and peripheral temperature, the score of shivering, nausea, pain, sedation vomiting incidence and drug complications was measured as entered in the recovery room and then every 10 min to an hour. Shivering grades was measured by crossly and Mahajan: 0 :No shivering, 1, piloerection or peripheral vasoconstriction but no visible shivering, 2 muscular activity in only one muscle group, 3 muscular activity in more than one muscle group, but not generalized shivering, 4 shivering involving the whole body.[12] In all patients, the basic value of parameters including the systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse rate (PR), and oxygen saturation (O_2 sat) was recorded from the time of entering in recovery every 10 min to an hour. All patients received routine post-operative nursing care. In case of the incidence of hypotension (reduction in systolic pressure below 100 mmHg or 25% decrease in systolic pressure to base pressure of patient), it was treated by 10 cc/kg Lactate Ringer and 5 mg intravenous ephedrine and if PR reduced below 55 beats, 0.01 mg/kg intravenous Atropine would be injected to the patient and if it was necessary, it would be repeated with the maximum of 0.04 mg/kg.

Shivering with a score of 3 or 4 or taking more than 15 min and nausea and vomiting were treated by Pethidine 25 mg and intravenous Ondansetron 4 mg, respectively. Pain was measured with visual analog scale and if patient had score 3 and higher was treated by 25 mg of intravenous Pethidine. After full awakening, the patient was extubated and the extubation time (from discontinuing anesthetic drugs until extubation of the trachea) and stay in the recovery room were also recorded. Furthermore, the duration of anesthesia, extubation time and discharge time from recovery were recorded according to discharge criteria of Aldrete score:[13]

Score assigned a number of 0, 1, or 2 to five variables: Activity, respiration, circulation, consciousness and color. A score of 9 out of 10 was considered adequate for discharge from the PACU. To ensure the double-blindness of this study, only the injector person knew about the type of the drug and the person collecting data didn't know anything about the type of injected drug. In addition to the mentioned data, demographic information and total required parameters were recorded in the questionnaire prepared in advance. Finally, the obtained data were entered and analyzed using the SPSS ver.20 and statistical *T*-test, Chi-square test and ANNOVA test by replicating the observations. The Chi-square test was used for comparison of qualitative data between two groups and *T* Student test used for comparison of quantitative data between two groups and repeated measured analysis of variance (ANOVA) for comparison of time series data between two groups.

RESULTS

In this study, a total of 66 patients were recruited to the study. Two of them were excluded [Figure 1]. Finally, 64 patients under surgery with general anesthesia were randomized between the two groups. The general and demographic information have been shown in Table 1. According to the obtained results, both groups had no significant differences in age, sex, ASA, weight, volume of received fluids, duration of surgery and anesthesia ($P > 0.05$).

The mean and standard deviation of hemodynamic parameters before induction to 1 h after entering to the recovery room have been shown in Table 2. Doing ANOVA test with replicating observations indicated that the mean of changes in blood pressure and the saturation percentage of blood oxygen didn't have any significant differences between both groups while HR changes indicated the significant differences. The

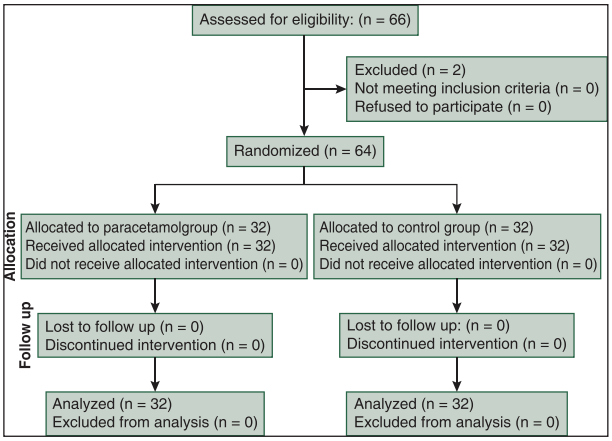

Figure 1: CONSORT diagram showing the flow of participants through each stage of the study

trend of changes in hemodynamic parameters between both groups has been shown in Figures 2-6.

The mean of changes in the core and peripheral temperature between two groups before induction to the end of staying in recovery has been shown in Table 3. Before intervention core and peripheral temperature were identical between the two groups ($P > 0.05$). ANOVA test with replicating observations on the mentioned data showed that in patients receiving Apotel, the core and peripheral temperature was significantly less than the control group during the

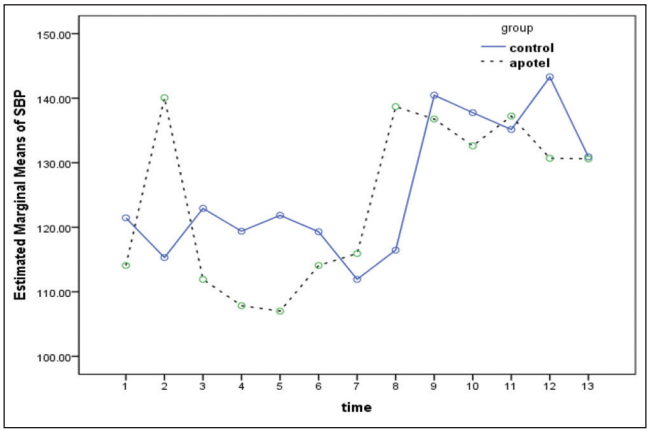

Figure 2: The trend of systolic blood pressure changes in both groups

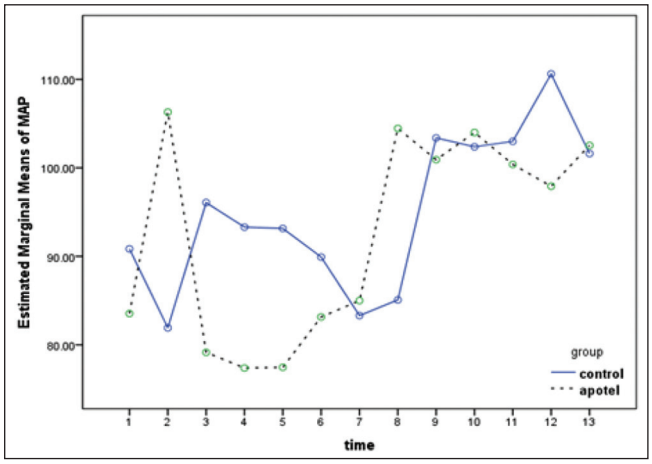

Figure 4: The trend of mean arterial pressure changes in both groups

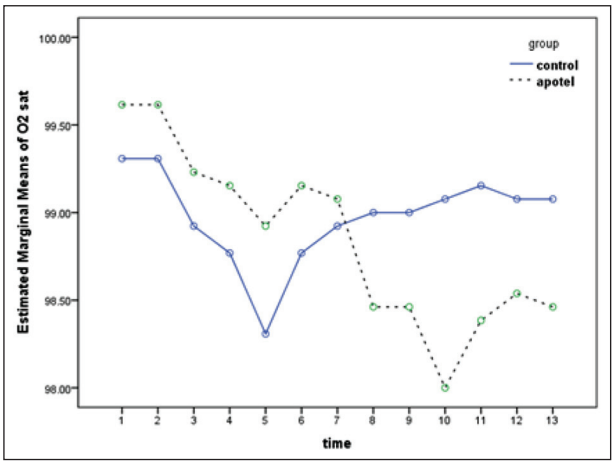

Figure 6: The trend of O2 sat changes in both groups

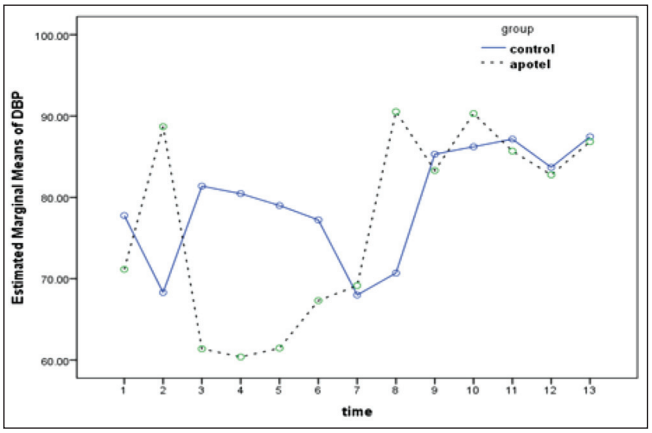

Figure 3: The trend of diastolic blood pressure changes in both groups

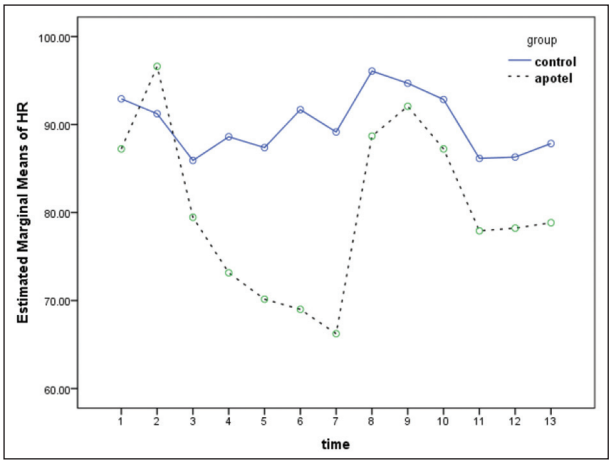

Figure 5: The trend of heart rate changes in both groups

Table 1: The distribution of demographic and general variables in both groups

Variable	Groups		*P*
	Intervention	Control	
Age (year)	8.38±4.16	9.33±14	0.21
Sex			
Male	8 (25)	6 (8.18)	0.55
Female	24 (75)	26 (2.81)	
ASA			
I	31 (9.96)	30 (8.93)	0.55
II	1 (1.3)	2 (2.6)	
Weight (kg)	5.71±9.8	6.74±7.9	0.18
Fluid volume (L)	29.1±4.0	28.1±4.0	0.88
Operation duration (min)	8.69±3.25	6.73±23	0.54
Anesthesia duration (min)	80±3.27	4.79±2.22	0.54

Data presented as mean ±SD or median (IQR) and number (percent); M: Male; F: Female; SD: Standard deviation; **P* values calculated by independent sample *t*-test; Mann-Whitney and Chi-square; IQR: Inter-quartile range; ASA: American Society of Anesthesiologists

intervention ($P < 0.05$). Figures 7 and 8 also show the trend of changes in the core and peripheral temperature in both groups.

The frequency distribution of the incidence of shivering from 0 until 60 min of entering patient into recovery showed that 10 individuals in the control group and 2 individuals in the intervention group suffered from shivering at 10 min after entering (31.2% vs. 6.2%) and according to Fisher exact test, the shivering was significantly higher in the control group ($P = 0.02$), however; in the rest of times, there was no significant difference between the two groups. In general, during the stay length of patients in recovery, 19 patients (29.7%) suffered from shivering that among them, 14 individuals were from the control group and 5 patients were in the intervention group (43.8% vs. 15.6%) and according to the Chi-square test, in the group receiving Apotel, the frequency distribution of shivering incidence in recovery was significantly less than the control group ($P = 0.014$). Furthermore, according to these results, in the control group, the risk of shivering incidence in recovery was 4.2 that in accordance with the related level of confidence, in the intervention group, the chance of shivering incidence was less than that in the control group (95% confidence interval = 1.025-13.7). The mean dose of pethidine in paracetamol receiving group in comparison with the case and control group was 21.4 ± 3.32 mg and 25.8 ± 4.5 mg respectively and according to *t*-test there was a significant difference between them ($P = 0.008$).

It should be noted that during the patient stay in the recovery room, only one patient in the control group suffered from nausea and vomiting at 40 min and the rest of times, in either group, no patient had nausea and vomiting. Furthermore, no patient suffered from drug complications during the study period.

In Table 4, the mean and standard deviation of pain intensity, sedation and the score of existing from recovery have been shown from arrival until 50 min

Table 2: Hemodynamic mean and standard deviation before indication until 1 h after entering in recovery room in both groups

Time/Variable	PT (Intervention)	PT (control)	CT (Intervention)	CT (Control)
Before induction	35.6±0.7	37.1±0.7	35.6±0.7	36.9±0.4
0 min	35.2±0.8	36.9±0.8	35.3±0.7	35.5±0.4
10 min	35.6±0.6	36.4±0.6	35.1±0.6	35.1±0.4
20 min	35.6±0.8	36±0.5	35±0.8	36.1±0.6
30 min	35.6±0.8	36±0.4	34.7±0.7	35.8±0.6
60 min	35.8±0.4	36.2±0.5	35.2±0.6	36.1±0.7
90 min	35.7±0.3	36.1±0.7	35.2±0.6	35.6±0.8
0 min recovery	35.8±0.4	36.2±0.4	34.9±0.7	35.6±0.9
10 min recovery	36±0.3	36.4±0.6	35.2±0.6	35.5±1
20 min recovery	36.1±0.3	36.4±0.5	35±0.4	35.5±0.8
30 min recovery	36.2±0.7	36.4±0.6	35.2±0.6	35.2±0.7
40 min recovery	36.4±0.3	36.5±0.6	35.2±0.7	35.5±0.7
50 min recovery	36.4±0.3	36.5±0.6	35.2±0.7	35.5±0.6
P value	<0.001		0.002	

PT :Peripheral Temperature; CT: Core temperature; Data presented as mean SD
$P < 0.05$ are significant

Table 3: The mean and standard deviation of the core and peripheral temperature before induction until 1 h after entering in recovery in both groups

Time	Group shivering	Control (%) number	Intervention number (%)	*P* value
Beginning the entrance	Without	31 (9.96)	32 (100)	0.99
	With	1 (1.3)	0 (0)	
10 min	Without	22 (8.68)	30 (8.93)	0.02
	With	10 (2.31)	2 (2.6)	
20 min	Without	29 (6.90)	29 (6.90)	1
	With	3 (4.9)	3 (4.9)	
30 min	Without	32 (100)	29 (6.90)	0.24
	With	0 (0)	3 (4.9)	
40 min	Without	32 (100)	32 (100)	1
	With	0 (0)	0 (0)	
50 min	Without	32 (100)	32 (100)	
	With	0 (0)	0 (0)	
60 min	Without	1 (9.96)	32 (100)	0.99
	With	1 (1.3)	0 (0)	
Total study time	Without	18 (2.56)	27 (4.84)	0.014
	With	14 (8.43)	5 (6.15)	

Data presented as number (percent); **P* value calculated by Chi-square test;
$P < 0.05$ is significant

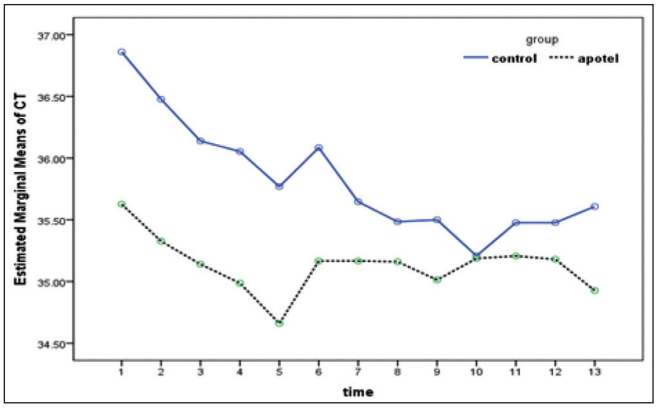

Figure 7: The trend of changes in the core temperature in both groups

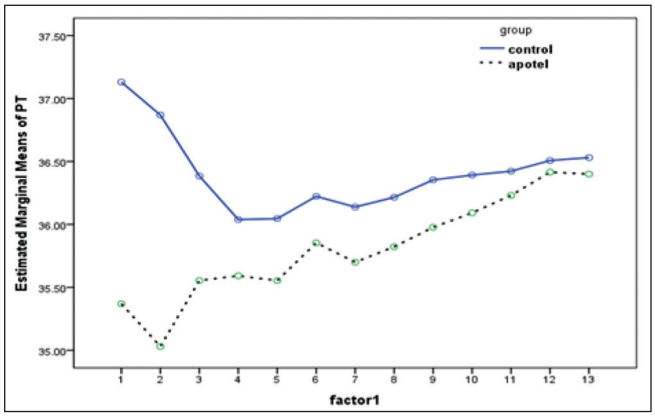

Figure 8: The trend of changes in the peripheral temperature in both groups

Table 4: The mean, standard deviation of pain intensity, sedation and the score of exiting from recovery in both groups

Variable time	Recovery discharge score		Sedation		Pain	
	Intervention	Control	Intervention	Control	Intervention	Control
0 min recovery	5.9±2	5.2±1	4.27±1	4.5±0.51	1.7±0.59	2.26±0.81
10 min recovery	6.9±1.9	6.5±1.5	3.89±1.2	3.43±0.9	1.69±0.47	2.3±0.79
20 min recovery	8.6±0.5	8±1.4	2.92±0.74	2.83±0.99	1.58±0.5	1.9±0.31
30 min recovery	9±0	8.5±1.3	2.35±0.49	2.33±0.88	1.42±0.5	1.37±0.49
40 min recovery	9.3±0.5	9±0.96	1.92±0.39	2.07±0.58	1.23±0.43	1.43±0.5
50 min recovery	9.5±0.51	9.2±0.55	1.81±0.4	1.97±0.41	1.15±0.38	1.43±0.05
P value	0.04		0.98		<0.001	

Data presented as number (percent); **P* value calculated by Chi-square test; $P < 0.05$ is significant

in both intervention and control groups. Doing ANOVA test with replicating observations showed that the mean of pain intensity in the group receiving Apotel was significantly lower than the control group during the duration of stay in recovery ($P < 0.001$). Furthermore, according to the above-mentioned test, patients receiving Apotel had a higher score for exit from recovery ($P = 0.04$) while in both groups, the mean of sedation had no significant differences during the stay in recovery ($P = 0.98$).

DISCUSSION

The main objective of this study was to determine the effect of intravenous paracetamol before inducting anesthesia on the changes in central and peripheral body temperature and intensity of shivering in patients undergoing general anesthesia. In this study, two groups of 32 patients each candidate for upper limb surgery under general anesthesia, were studied. The two groups in terms of basic and demographic variables of age, sex, ASA, weight, fluid volume, operation time and length of stay in the recovery we're not significantly different. The confounding effect of these factors in this study was neutralized and the observed differences are likely due to the taken drug. Furthermore, given the obtained results, patient vital variables did not differ in terms of blood pressure and blood oxygen saturation. In other words, during anesthesia and recovery duration, taking Apotel had not adverse effect on the blood pressure of patients; however, changes in heart rate was significantly different in both groups and during this time, patients receiving Apotel had lower heart rate that the finding is likely due to reducing the pain intensity due to Apotel.

According to the results obtained from our study, patients receiving Apotel had lower core and peripheral temperatures than the control group which is consistent with the findings of other studies. In Stevonst *et al*. study on pediatric cardiac surgery, the prescription of 650 mg acetaminophen in normothermic individuals had significant effects on the core body temperature or starting Hypothermia.[14] Furthermore, in J van study conducted on stroke patients, daily using 6000 mg of Paracetamol has significantly reduced the body temperature after ischemic stroke while in Scotte study on stroke patients receiving 3900 mg of Paracetamol, Hypothermia had become more severe.[14,15]

The incidence of shivering in recovery room was another factor evaluated in the present study and during the patient stay in the recovery room, 43.8% of patients in the control group and 15.6% of patients receiving Apotel suffered from shivering and using Apotel could reduce the chance of incidence at the amount of 4.1 times due to Apotel effect on hypothalamus and the core body temperature that its mechanism is in hyperthermia by affecting on the synthesis of Prostaglandin.[14,15]

According to the results obtained from our study, patients receiving Apotel had less post-operative pain intensity than the control group and their score exiting from recovery was higher and also Apotel significantly affected post-operative pain, the score of recovery discharging, shortening the duration of stay in recovery and lowering extubation time. According to the results obtained from our study, patients receiving Apotel had less post-operative pain intensity than the control group and their score exiting from recovery was higher and also Apotel significantly affected post-operative pain, the score of recovery discharging, shortening the duration of stay in recovery and lowering extubation time. Hence, considering the beneficial effects and complications of Apotel, which mainly include reducing post-operative shivering and pain, using this drug as a pre-drug is recommended for patients under surgery with general anesthesia.

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