



# Effects of Inadvertent Perioperative Hypothermia on Metabolic and Inflammatory Mediators

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## Abstract

**Objective:** The aim of the present study was to investigate the effects of perioperative undesirable hypothermia on inflammatory (interleukin (IL)-8, IL-10, IL-18, IL-23 and pentraxin (PTX)-3) and metabolic responses (cortisol and insulin) and recovery time.

**Methods:** A total of 60 patients between the ages of 18 and 65 years who were in the lumbar stabilisation operation were included in the study. In this prospective, randomised controlled study, two groups were constituted as with warmed (Group N) and not warmed (Group C) patients before and during the operation. Diuresis, blood loss, body temperature and side effects were recorded with IL-8, IL-10, IL-18, IL-23, PTX-3, cortisol and insulin levels.

**Results:** Perioperative diuresis was significantly higher in Group C. Aldrete score was significantly higher in Group N with less shivering and vomiting in the postoperative period. IL-10, PTX-3 and cortisol levels were found to be significantly higher in Group C in the first postoperative hour. PTX-3 and cortisol were found to be significantly higher in Group C after 24 h of the operation. Insulin was significantly higher in Group N. In 72 h, IL-8 in Group N and cortisol level in Group C were significantly higher.

**Conclusion:** Positive effects of heating the patients in the perioperative period on haemorrhage, diuresis, complications and recovery time were observed in our study. In addition, maintenance of normothermia appeared to modulate the biomarkers that indicate the inflammatory and metabolic responses.

**Keywords:** Cortisol, hypothermia, inflammation mediators, insulin

## Introduction

Perioperative heat loss is related to many factors, such as age, gender, body surface, type and duration of operation, operating room temperature and application of mechanical ventilation. Anaesthetic agents inhibit the hypothalamus in patients under general anaesthesia, increasing the body temperature regulation range from 0.2°C to 4°C and delaying the thermoregulatory response (1).

Accidental perioperative hypothermia may lead to prolongation of the duration of action of hypnotic drugs and neuromuscular blockers, increases in blood transfusions due to increased intraoperative blood loss, development of cardiac problems that may increase mortality, prolonged recovery times after anaesthesia, increased oxygen consumption accompanying shivering, facilitate surgical site infections, increased incidence of vomiting and prolongation of hospital stay (2-5).

There are limited data on the modulation of metabolic and inflammatory process mediators related to perioperative hypothermia. The aim of the present study was to investigate the effects of perioperative inadvertent hypothermia

on interleukin (IL)-8, IL-10, IL-18, IL-23, pentraxin (PTX)-3 and metabolic responses (cortisol and insulin).

## Methods

In this prospective randomised controlled study, two groups were constituted as control (Group C) and normothermia (Group N). A total of 60 patients underwent the same method of anaesthesia and surgical operation. Patients undergoing elective lumbar stabilisation surgery lasting >2 h were included in the study. The study was approved by the ethics committee of the Çanakkale Onsekiz Mart University Faculty of Medicine (application no. 2011-KAEK-27/2015-128). The project was funded by the University Scientific Research Projects (BAP) (grant no. 2015-733). Patients were informed about the study. Informed consent was obtained from the patients. Patients participating in the study were randomly divided into groups using the closed envelope method. Patients were selected between the ages of 18 and 65 years and with American Society of Anesthesiologists (ASA) I-II group. Patients with unregulated chronic systemic disease, systemic infection, pregnancy and mental retardation were excluded from the study.

In contrast to the control group, the operation table was heated to 38°C with a pneumatic blanket before the patient's arrival in the normothermia group. The infusions were heated to 36.5°C before intravenous (iv) administration during the operation in the normothermia group. Infrared thermometer was used with the body temperature of the tympanic membrane measured. First, measurements of body temperatures of both patient groups were performed in the surgery clinic room, and measurements were continued in the operating room after monitoring and before the induction of anaesthesia. Midazolam (0.01 mg kg<sup>-1</sup>), fentanyl (1 µg kg<sup>-1</sup>), lidocaine (1 mg kg<sup>-1</sup>), propofol (2-2.5 mg kg<sup>-1</sup>) and rocuronium (0.6 mg kg<sup>-1</sup>) were administered iv for induction of anaesthesia. Urinary catheter was inserted after endotracheal intubation. Then, body temperature measurements were obtained at 5, 10 and 15 min. After the induction, measurements continued every 15 min. Other vital data were noted at the same time interval. Urinary output and blood loss were recorded every 30 min during the operation. Total blood loss, transfusions, urinary output and duration of surgery were recorded after the operation. Modified Aldrete scores were calculated in the postoperative period.

### Laboratory analysis

After the operation for 1, 24 and 72 h, blood samples were collected to vacuum gel tubes for biochemical analysis of inflammatory mediators, such as IL-8, IL-10, IL-18, IL-23 and PTX, and hormonal analysis of cortisol and insulin.

The samples were incubated at room temperature of 25°C for 30 min and then centrifuged at 4000 rpm for 10 min.

Sera from blood samples for PTX-3, IL-18, IL-23, IL-10, IL-8, cortisol and insulin were separated and stored at -20°C until the study day. No more freeze-thawing was implemented for samples. Cortisol and insulin were studied by electrochemiluminescence method using Cobas 6000 e601 analyser with Roche kits (Roche Diagnostics GmbH, Mannheim, Germany).

PTX-3 (cat. no.: 201-12-1939; Sunred Biological Technology, Shanghai, China), IL-18 (cat. no.: 201-12-0148; Sunred Biological Technology), IL-23 (cat. no.: 201-12-0075; Sunred Biological Technology), IL-10 (cat. no.: 201-12-0103; Sunred Biological Technology) and IL-8 (cat. no.: 201-12-0090; Sunred Biological Technology) levels in serum were measured by using commercial kits based on the quantitative sandwich enzyme-linked immunosorbent assay (ELISA) method. The results were determined by reading the ELX 808 IU model ELISA reader. The coefficient of variation, variation coefficient values intraday and between days for PTX-3, IL-18, IL-23, IL-10 and IL-8 were determined as <10% to <12%.

### Statistical analysis

Statistical analysis was performed by using the Statistical Package for the Social Sciences software version 20 (IBM SPSS Statistics Armonk, NY, USA). Shapiro-Wilk test was used to assess the normal distribution of continuous variables. Mean, standard deviation and frequency values were used in the presentation of descriptive data. Mann-Whitney U test was used for variables that are not normally distributed, and t-test was used for variables with normal distribution in comparisons between independent groups. Chi-square test was used in the univariate analysis of dependent and independent variables. A p-value<0.05 was considered statistically significant.

## Results

A total of 60 patients were included in the study. There were 8 male and 22 female patients in Group N and 9 male and 21 female patients in Group C. Age, gender, ASA score, body mass index, total amount of haemorrhage, total fluid and blood transfusions during the operation were compared between the groups, and there was no statistically significant difference between the groups (Table 1).

Operation times were recorded in both groups and determined as 212.0±20.4 min for Group N and 206.1±36.8 min for Group C. There was no statistical difference between the groups. The mean total urinary output of the patients during the operation was 200±207 mL in Group N and 370±282 mL in Group C. There was a statistically significant higher urine output in Group C (p<0.001). Body temperature mea-

**Table 1. Demographic characteristics of the patients.**

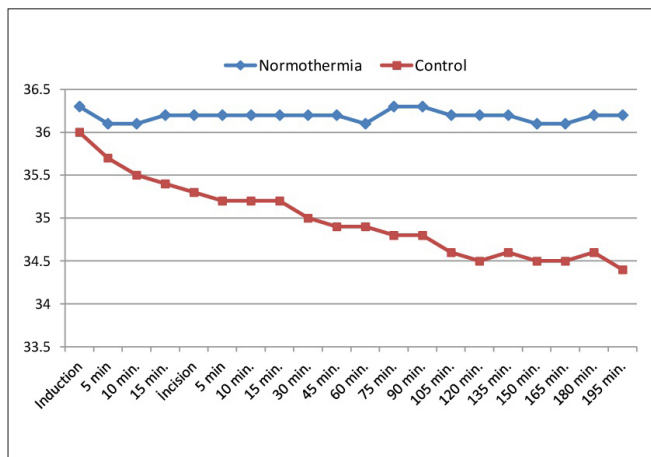
Variables	Group N (n=30)	Group C (n=30)	p
	n (%)	n (%)	
Female	22 (73.3)	21 (70.0)	0.774
Male	8 (26.7)	9 (30.0)	
<b>ASA</b>			0.100
I	13 (43.3)	7 (23.3)	
II	17 (56.7)	23 (76.7)	
<b>Complications</b>			0.080
No	25 (83.3)	19 (63.3)	
Yes	5 (16.7)	11 (36.7)	
	<b>Mean±SD</b>	<b>Mean±SD</b>	<b>p</b>
Age	55.7±2.0	56.9±1.7	0.693
BMI	31.4±0.7	29.8±0.8	0.156

ASA: American Society of Anesthesiologists; BMI: body mass index; SD: standard deviation

**Table 2. Comparison of postoperative first hour IL, PTX-3, insulin and cortisol parameters between the groups**

Variables	Group N (n=30)	Group C (n=30)	p
IL-8	53.3±71.77	42.2±58.5	0.464
IL-10	863.6±884.0	1056.4±847.5	0.006
IL-18	25.4±24.69	23.4±21.6	0.888
IL-23	46.5±40.3	40.3±29.2	0.976
PTX-3	3.6±3.2	7.7±6.0	0.000
Cortisol	13.1±8.8	26.5±10.6	0.000
Insulin	22.4±23.4	14.6±10.0	0.237

p: Wilcoxon signed-rank test. IL: interleukin; PTX-3: pentraxin-3



**Figure 1. Body temperature changes in both groups with the duration of operation**

measurements in the postoperative first hour were 36.5±0.2°C in Group N and 36.3±0.2°C in Group C (p=0.008), and the difference was statistically significant (p=0.008).

There was a statistically significant difference between the two groups when the body temperature values were compared

during the operation (p<0.001) (Figure 1). The lowest temperatures in both groups were seen at 195 min during the operation. The lowest temperature in Group N was 36.2±0.41°C, whereas the lowest temperature in Group C was 34.37±0.46°C.

There was no statistically significant difference between the preoperative measurements of IL-8, IL-10, IL-18, IL-23, PTX-3, insulin and cortisol parameters in both groups. Group C had statistically significantly higher values of IL-10, PTX-3 and cortisol, respectively, levels in the first hour of operation (p<0.01) (Table 2).

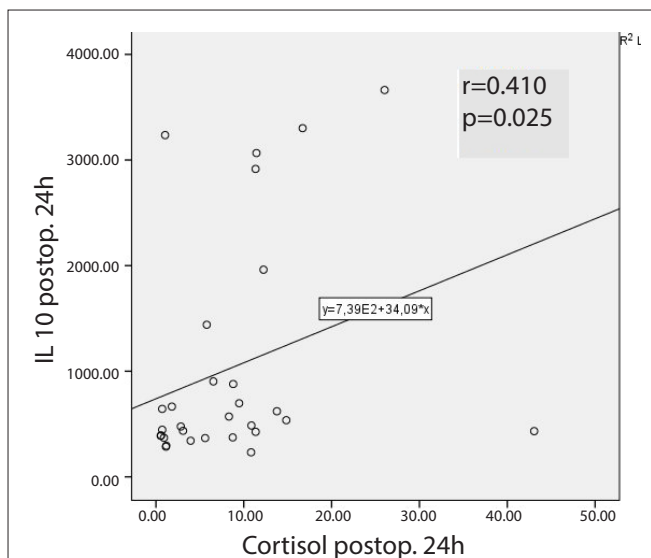
There was a statistically significant increase in the values of PTX-3 and cortisol (p=0.013) in Group C for 24 h of the postoperative period. Insulin levels were found to be significantly higher in Group N 24 h after the operation (p=0.007). IL-8 levels were found to be higher in Group N than in Group C, which was statistically significant at postoperative 72 h. Cortisol levels were significantly higher in Group C at postoperative 72 h (p=0.002) (Table 3).

IL-8 was statistically significantly higher in Group C than in Group N at postoperative 72 h (p=0.044). Cortisol levels were

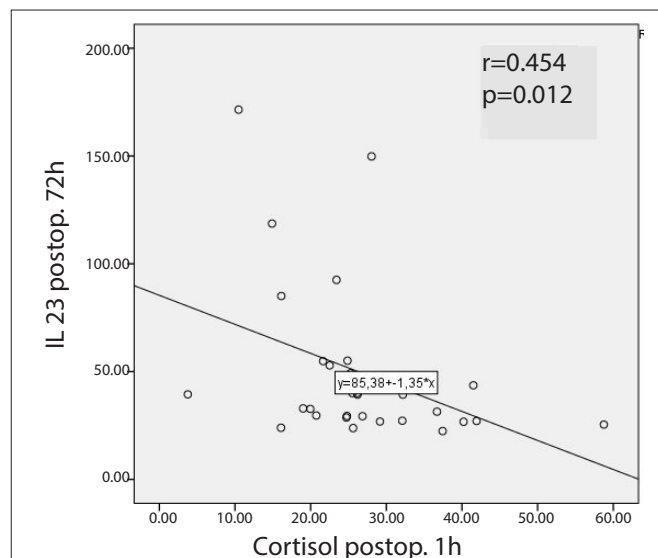
**Table 3. Comparison of postoperative 24 and 72 h IL, PTX-3, insulin and cortisol parameters in both groups**

Variables (h)	Group N (n=30)	Group C (n=30)	p
IL-8 (24)	63.5±88.2	38.5±56.2	0.48
IL-8 (72)	78.4±100.5	52.1±71.6	0.044
IL-10 (24)	1028.2±1068.2	967.17±925.4	0.072
IL-10 (72)	1188.3±1066.0	1227.7±1111.2	0.156
IL-18 (24)	30.9±29.5	20.8±20.0	0.049
IL-18 (72)	32.8±27.2	27.1±23.9	0.610
IL-23 (24)	52.6±45.9	39.2±31.8	0.734
IL-23 (72)	62.4±51.3	49.6±37.4	0.959
PTX-3 (24)	4.4±4.0	7.4±5.7	0.009
PTX-3 (72)	5.5±4.3	8.1±5.2	0.13
Cortisol (24)	8.4±8.9	16.1±14.8	0.013
Cortisol (72)	8.1±6.4	14.0±9.5	0.002
Insulin (24)	48.3±38.1	23.1±15.2	0.007
Insulin (72)	31.0±28.0	29.6±26.3	0.947

p: Wilcoxon signed-rank test. IL: interleukin; PTX-3: pentraxin-3



**Figure 2. Correlation of cortisol with IL-10 (postoperative 24 h) in the normothermia group**



**Figure 3. Correlation of cortisol with IL-23 (postoperative 72 h) in the control group**

significantly higher in Group C (p=0.002) 72 h after the operation (p=0.002) (Table 3).

Correlations between cortisol and other parameters in the normothermia group were analysed, and a positive correlation was detected between 24-hour cortisol and 24-hour IL-10 levels (r=0.410, p=0.025) (Figure 2).

When the correlations between cortisol and other parameters were analysed in the control group, an inverse correlation was found between postoperative first hour cortisol and 72-hour IL-23 (r=0.454, p=0.012), a positive correlation was found between 72-hour cortisol and first hour IL-8 (r=0.378, p=0.039), and a positive correlation was found between 72-

hour cortisol and 72-hour IL-18 (r=0.366, p=0.047) (Figures 3-5).

Patient recovery was assessed at 5-minute intervals using a modified Aldrete score. Modified Aldrete score was 10 points at 5 min in the normothermia group, whereas this score was achieved at 15 min in Group C. There was a statistically significant difference between the groups according to total patients reached to 10 modified Aldrete scores of both groups at 10 min (p=0.025).

There was no difference in postoperative hypotension, bradycardia and vomiting rates in both groups of patients. Shivering and nausea rates were found to be significantly higher in the control group (p<0.05) (Table 4).

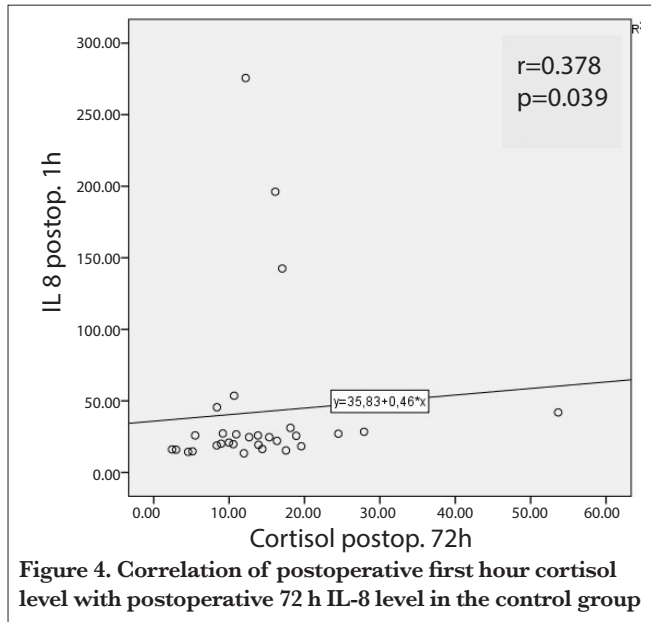


Figure 4. Correlation of postoperative first hour cortisol level with postoperative 72 h IL-8 level in the control group

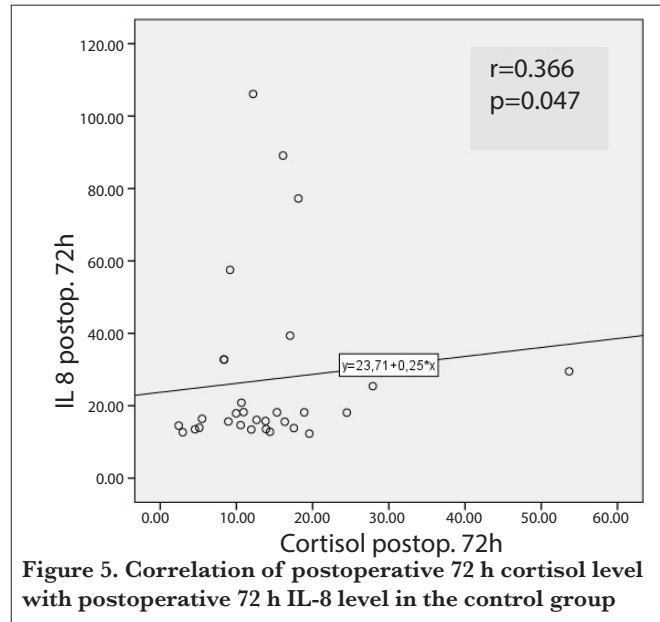


Figure 5. Correlation of postoperative 72 h cortisol level with postoperative 72 h IL-8 level in the control group

Variables	Group N, n (%)	Group C, n (%)	p
Hypotension	3 (10)	7 (23.3)	0.149
Bradycardia	1 (3.3)	0 (0.0)	0.315
Nausea	10 (33.3)	18 (60)	0.035
Vomiting	8 (26.7)	10 (33.3)	0.389
Shivering	6 (20.0)	20 (66.7)	<0.001

p: chi-square test

### Discussion

In our study, we observed that patients heated perioperatively had better recovery and less postoperative complications. Cortisol and insulin values assessed as stress response markers were identified to be better in the group heated during the perioperative period. Additionally, the postoperative inflammatory response was observed to be at lower levels in the heated group. Though many studies have reported that serious complications are observed to be linked to perioperative hypothermia and hypothermia development, temperature monitoring and management have not seen sufficient interest in clinical applications. A study of 8083 surgical patients in 17 countries in Europe reported that only 19% of the patients had temperature monitoring, and that only 38% had active heating precautions taken (6). El-Gamal et al. (7) reported that a temperature of the operating room <23°C is a risk factor for hypothermia, and that temperatures >26°C largely reduce the prevalence of hypothermia; however, this situation may be uncomfortable for medical personnel and increase the possibility of surgical site infection. In our study, initially, the operating room temperature was set to 23°C. However, the operating room temperature was checked at intervals as

21°C-24°C. If we assume that the mean temperature of our operating room is 21°C, there was no difference identified between the room temperatures for the two groups in our study.

When deciding on the location for temperature monitoring, due to the appropriateness of the patient position and the reliability of central temperature measurement (8), an infrared thermometer was used with the body temperature of the tympanic membrane measured. The perioperative temperature value was 35.9±0.5°C in Group N, whereas this was 35.3±0.5°C in Group C in the first minutes of the operation. While the progressive decrease in body temperature over time continued in Group C, at 195 min, the body temperature was 34.7±0.5°C. When all perioperative measurements are compared, Group N had significantly higher temperature values than Group C. In spite of active heating of Group N, the temperature increased to a maximum of 36.3°C-36.7°C, whereas the maximum in Group C was 34.4°C-35.8°C. Body temperature measurements in the postoperative first hour were significantly higher in Group N than in Group C although the difference was clinically not significant. This result could provide an opinion that control group patients are delaying to achieve normothermic condition during the postoperative period.

Mild hypothermia was shown to significantly delay discharge of adult patients from the recovery unit (9). In our study, recovery from anaesthesia was assessed by the modified Aldrete's scoring system. When the modified Aldrete score is compared at 0 and 5 min, the score of the normothermia group was observed to be significantly high. With the modified Aldrete score of 10 used as a discharge criteria for the recovery unit, there were more patients with this score in Group N than in Group C at 10 min. Additionally, at the end of 15 min, all patients had an Aldrete score of 10. Finally, considering that Group N recovered from general anaesthesia and discharged from post-anaesthesia care unit (PACU) more quickly, it appears that the duration in the PACU for patients in Group N was 5-10 min shorter than that in Group C.

Shivering is one of the important complications of hypothermia (10). It is reported that not all shivering is due to hypothermia but may be associated with different causes (11). In our study, postoperative shivering was observed in 6 patients in Group N and 20 patients in Group C. As comorbid causes were excluded for patients included in the study, the significantly more common observation of shivering in Group C was associated with hypothermia.

Studies assessing postoperative patients have observed that hypothermia disrupts wound healing and increases hospital stays for 20% (12, 13). Vasoconstriction for thermoregulation significantly reduces the subcutaneous oxygen pressure in humans (14), and the incidence of wound infections is correlated with subcutaneous oxygen pressure (15). Additionally, hypothermia affects T cell-mediated antibody production and the non-specific oxidative bacteria killing functions of neutrophils, directly disrupting immune functions. Fröhlich et al. (16) reported that hypothermia may reduce neutrophil function in the early stage of infection. In our study, we indirectly compared the wound healing durations based on the discharge from hospital times of the two groups and found no statistically significant difference, though the mean hospital stay of the control group was observed to be 1.5 days longer.

In our study, the inflammatory cytokine levels were measured in both patient groups at certain intervals. The cytokines selected in the present study were the anti-inflammatory cytokine IL-10, IL-8 known as a chemotactic cytokine, IL-18 in the IL-1 family and produced by macrophages and other cells and IL-23 triggering both neutrophil flow and proinflammatory cytokine production during acute infection and contributing to the accumulation of neutrophils in the infection region. Additionally, due to the stress response and the known effects of hypothermia on the adrenal axis, cortisol and insulin levels were simultaneously studied in the same serum samples.

Xiao et al. (17) induced sepsis with caecal ligation and puncture in an experimental study and postoperatively warmed mice exposed to perioperative hypothermia linked to anaesthesia. Then, both groups were investigated, and there was a decrease in IL-6 levels reflecting the reduction in inflammatory response due to heating; however, they reported that the inflammatory response is not completely suppressed.

An in vitro study proposed that mild hypothermia could increase IL-1, IL-6, IL-12 and tumour necrosis factor- $\alpha$  levels activating inflammation (18). However, some experimental studies have contrarily reported that hypothermia causes a reduction in inflammation (19, 20).

The experimental data related to the effect of hypothermia on IL-10 levels are contradictory. Matsui et al. (21) revealed that IL-10 production reduces with hypothermia, whereas microglia culture from hypothermic neonatal rats reveals that hypothermia strengthens IL-10 production. Additionally, another study identified that paediatric patients treated with moderate hypothermia after traumatic brain injury had higher IL-10 levels (22).

Yenari et al. (23) reported that short-duration (2-4 h) hypothermia increases anti-inflammatory cytokine levels (IL-4 and IL-10); however, hypothermia lasting for periods >24 h causes a reducing trend in cytokine concentrations. Róka et al. (24), in a study of 18 newborns with perinatal asphyxia-linked hypoxic ischaemic encephalopathy, considered that therapeutic hypothermia reduces the early increase in IL-6 levels especially in the first 24 h following perinatal asphyxia and suppresses the hypoxia-linked inflammatory response. In our study, comparisons between the groups found no statistically significant difference with respect to preoperative IL-8, IL-10, IL-18, IL-23, PTX-3 and cortisol values. However, IL-10, PTX-3 and cortisol values at postoperative 1 h, PTX-3 and cortisol values at postoperative 24 h and cortisol values at postoperative 72 h were statistically significantly high in Group C. Insulin at postoperative 24 h and IL-8 values at postoperative 72 h were statistically significantly higher in Group N than in the other groups.

Glucocorticoids play an important role in the physiology of stress response (25). Pinto et al. (26) reported a negative correlation between cytokine release and cortisol concentrations. Different studies reported a correlation between general anaesthesia duration and cortisol concentration (27). In our study, a comparison between Group N and Group C found similar preoperative cortisol levels, whereas at postoperative 1, 24 and 72 h, cortisol was statistically significantly high in Group C. When the correlation between cortisol and the other parameters is investigated, in Group C, there were an inverse correlation between postoperative 1-hour cortisol

and 72-hour IL-23, a positive correlation between 72-hour cortisol with 1-hour IL-8, and a positive correlation between 72-hour cortisol and 72-hour IL-18. In Group N, there was a positive correlation between 24-hour cortisol and 24-hour IL-10 ( $r=0.410$ ,  $r=0.025$ ) observed.

With sympathetic activation linked to surgical stress and increased catecholamine, insulin release firstly reduces and then increases with biphasic progression (28). Curry et al. (29) investigated the effects of hypothermia of isolated rat pancreas on insulin release in an experimental study and showed that hypothermia directly inhibits insulin release. In their study, reheating did not easily reverse inhibition, and >30-minute delays were present in returning to the normal secretion process (29). In our study, at postoperative 24 h, insulin in Group N was statistically significantly higher than that in Group C.

There is no study found in the literature about the association of PTX-3, with an important place in the acute phase of the inflammatory response and hypothermia. Though it plays an important place in the inflammatory process, control group values for PTX-3 in the study were found to be significantly higher at postoperative 1 and 24 h than the normothermia group.

## Conclusion

In our study, heating or trying to keep patients normothermic in the perioperative period for patients with lumbar stabilisation surgery appeared to have lower side effect profile and ensure more balanced haemodynamic parameters. It is considered that heated patients have healthier perioperative immune modulation, and as a result, wound healing will be more rapid, and length of hospital stay will be reduced. Especially in critical patients, more controlled release of stress hormones will reduce the incidence of unwanted complications.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Çanakkale Onsekiz Mart University (Date: 21.01.2015; application no. 2011-KAEK-27/2015-128).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – Y.D., H.A.; Design – T.Ş., H.A.; Supervision – Y.D.; Resources – H.A., Y.D.; Materials – H.A.; Data Collection and/or Processing – T.Ş., Y.D.; Analysis and/or Interpretation – T.Ş., H.A.; Literature Search – H.A.; Writing Manuscript – H.A., T.Ş.; Critical Review – T.Ş., Y.D.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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