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Effects of intraoperative hypothermia on stress hormone response in surgical patients

Uticaj intraoperativne hipotermije na hormonski odgovor na stres kod hirurških bolesnika

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Abstract

Background/Aim. Surgical stress itself, as well as hypothermia induced by general anesthesia and low ambient temperature, activates stress hormone response with changes in catecholamines and counter-regulatory hormones. The aim of this study was to investigate the acute hormone stress response in patients who underwent major surgical procedures and the efficiency of external and internal warming methods in alleviating these changes. **Methods.** The study included a total of 60 patients who underwent major open abdominal surgical procedures and were randomly divided into 4 groups: control non-warmed (C), externally warmed using forced-air warming mattress (W), internally warmed using intravenous amino acids (A), and warmed with a combination of external and internal method (A+W). Esophageal temperature was used as a measure of core temperature. Concentrations of epinephrine, norepinephrine, cortisol, prolactin, and testosterone were measured. Blood samples for hormone measurement were obtained at two time points for catecholamines – 90 min before and 120 min after finishing the surgery, and at additional two-time points for cortisol, prolactin, and testosterone (24 and 48 hrs after surgery). **Results**. In the W and A+W groups, the temperatures did not significantly differ between time points but constantly decreased in the C and A groups, with a statistically significant difference between the anesthesia induction and the 120th min (35.61 ± 042 vs. 33.86 ± 0.71 °C; $p < 0.000$ and 35.81 ± 0.54 vs. 34.45 ± 0.41 °C; $p < 0.000$, respectively). Catecholamine concentrations in all groups showed a significant increase during surgery, with the highest values recorded in the non-warmed group (777.07 ± 800.08 after vs. 106.13 ± 89.63 pg/mL before surgery for epinephrine and 1,349.67 ± 984.16 vs. 580.53 ± 465.38 for norepinephrine, $p < 0.000$). Concentrations of cortisol and prolactin also showed a significant increase at the same time point, with a tendency to normalize after 48 hrs. On the contrary, testosterone concentrations showed a decrease after 120 min without normalization throughout the entire period of observation. Except for testosterone, changes in all stress hormones were attenuated in warmed groups compared to controls. **Conclusions**. Regarding both features of surgical stress investigated in this study (hypothermia and stress hormone response), the combination of endogenous amino acid-induced thermogenesis and external air warming mattress is most effective in its prevention.

Key words:
anesthesia, general; body temperature; hormones; hypothermia; intraoperative complications; stress, physiological; surgical procedures, operative.

Apstrakt

Uvod/Cilj. Hirurški stress sam po sebi, kao i u kombinaciji sa hipotermijom izazvanom dejstvom opšte anestezije, pokreće hormonski odgovor na stres koji karakterišu promene u nivoima kateholamina i drugih regulatornih hormona. Cilj rada bio je da se utvrdi akutni hormonski odgovor na stres kod bolesnika podvrgnutih dugotrajnim hirurškim intervencijama, kao i da se ispita efikasnost spoljašnjeg i unutrašnjeg zagrevanja u ublažavanju tih promena. **Metode**. Istraživanjem je obuhvaćeno ukupno 60 bolesnika podvrgnutih velikim hirurškim intervencijama na otvorenom abdomenu, koji su nasumično podeljeni u 4 grupe: kontrolnu koja nije dodatno zagrevana (C), grupu koja je zagrevana madracem sa toplim vazduhom (W), grupu koja je zagrevana infuzijom aminokiselina (A) i grupu koja je zagrevana kombinacijom te dve metode (A+W). Unutrašnja temperatura merena je ezofagealnom sondom. Ispitivana je koncentracija adrenalina, noradreanlina, kortizola, prolaktina i testosterona. Uzorci krvi uzimani su 90 min pre i 120 min posle završetka hirurške procedure (za kateholamine), a u dodatna dva termina za ostale hormone (24 i 48 sata nakon završetka operacije). **Rezultati.** U W i A+W grupi temperatura se nije razlikovala tokom perioda praćenja, dok se u C i A grupi konstantno snižavala, sa statistički značajnom razlikom između momenta uvođenja u anesteziju i 120 min

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posle operacije (35,61 ± 0,42 vs. 33,86 ± 0,71 °C; $p < 0,000$, odnosno 35,81 ± 0,54 vs. 34,45 ± 0,41 °C; $p < 0,000$). Koncentracija kateholamina je u svim grupama značajno porasla tokom operacije, a najviše vrednosti izmerene su u nezagrevanoj grupi (777,07 ± 800,08 vs. 106,13 ± 89,63 pg/mL za adrenalin i 1349,67 ± 984,16 vs. 580,53 ± 465,38 za noradrenalin, $p < 0,000$). Koncentracije kortizola i prolaktina takođe su porasle u istim intervalima, sa tendencijom normalizacije nakon 48 sati. Naprotiv, koncentracije testosterona značajno su se snižavale posle 120 min i niske vrednosti su se održavale kroz ceo period praćenja (48 sati). Osim u slučaju testosterona, promene svih ostalih hormona ublažene su kod zagrevanih bolesnika u poređenju sa kontrolnom grupom. **Zaključak**. Posmatranjem obe ispitivane karakteristike hirurškog stresa (hipotermija i hormonski odgovor na stres), utvrđeno je da je u njegovoj prevenciji najefikasnija kombinacija endogenog zagrevanja aminokiselinama i spoljašnjeg zagrevanja madracem sa toplim vazduhom.

Ključne reči:
anestezija, opšta; telesna temperatura; hormoni; hipotermija; intraoperativne komplikacije; stres, fiziološki; hirurgija, operativne procedure.

Introduction

Low ambient temperature in the operation theatre and prolonged effects of general anesthesia may lead to intra- and postoperative hypothermia in surgical patients. Complications of hypothermia in these patients are recognized as cardiovascular and respiratory dysfunction, impairment of the coagulation system, and coagulopathy [1]. Hypothermia during major surgical interventions may be prevented using several external warming methods, as well as internal administration of warm fluids with various compositions. The result of such interventions in literature are rather controversial, which may be contributed to the type of anesthesia, type of surgery, patient's age, and comorbidity. In our previous studies, the efficacy of two methods for preventing intraoperative hypothermia was investigated [2, 3]. The results indicated that both external warming (using air-forced warming mattress) and internal warming (administration of amino acid solutions) attenuate perioperative hypothermia.

Response to surgical stress is related to cellular and tissue injuries and nociceptive stimulation which influence hormonal and metabolic processes by activating the hypothalamic-pituitary-adrenal axis and secretion of stress hormones. In addition to surgical stress, the secretion of catecholamines is also induced by hypothermia in order to increase metabolic thermogenesis [4]. High cortisol and prolactin concentrations are common immediately after and up to 4–6 days following surgical procedures. On the other hand, concentrations of testosterone decrease after surgery, and low levels may be sustained for several days, which may delay anabolic processes [5].

Considering the importance of stress response in surgical patients, as well as the impairment of anabolic hormonal activity, the aim of our study was to investigate whether maintaining intraoperative normothermia using external and/or internal warming methods could influence stress response in patients who underwent major open abdominal surgical procedures.

Methods

The study population comprises 60 patients who underwent major open abdominal surgical procedures (between 2 and 4 hrs). The investigation was conducted at the Military Medical Academy in Belgrade, Serbia designed as a single-center prospective controlled interventional study according to ethical principles for investigations in biomedical science. Each participant signed informed consent. The study included adult patients with American Society of Anesthesiologists (ASA) score I or II who underwent elective colorectal surgical procedures for malignancy. Of 124 patients initially considered for enrolment, 64 were excluded according to criteria as follows: other indication than colorectal malignancy, ASA score III or IV, duration of intervention less than 2 hrs or more than 4 hrs, and administration of blood transfusion during surgery.

In all patients, the same method of general balanced anesthesia (GBA) was used. For premedication, 10 mg of diazepam (intramuscular – IM injection) was administered one h before anesthesia induction. Midazolam [0.05–0.15 mg/kg of body weight (BW)], fentanyl (2–6 μg/kg BW), propofol (1–2.5 mg/kg BW), and rocuronium (0.6-1mg/kg BW) were used for induction of GBA. Anesthesia and analgesia were maintained with 2–4 vol% of volatile esthetic sevoflurane (respiratory volume of 6–8 mL/kg BW) with an intermittent bolus of 25–50 μg of fentanyl. Neuromuscular blockade was maintained with an intermittent bolus of 0.15 mg/kg BW of rocuronium. No difference was registered between groups regarding hemodynamic parameters or volume loading, regardless of the warming method. Every patient was treated identically, according to contemporary guidelines.

A detailed description of methods of body temperature measurements (esophageal and skin temperatures) is presented in our previous study [3]. Patients were randomly divided into 4 groups: control group (C) consisted of 15 non-warmed patients, while in the other 3 groups, the same number of patients were either warmed externally (W group) using forced-air warming mattresses as described in the previous study [3], either received iv amino acids intraoperatively (A group), or combination of amino acids and external warming (A + W group). In the latter 2 groups, a commercial solution of 18 amino acids (Aminosol® 15%, Hemofarm AD, Serbia) was administered *via* a central venous catheter at a rate of 125 mL/h immediately after anesthesia induction in order to provide internal thermogenesis [2].

Blood samples for hormone measurement were obtained from each patient at two-time points for epinephrine and norepinephrine: 90 min before and 120 min after finishing the surgery, and at four-time points for cortisol, prolactin, and testosterone: 90 min before and 120 min, 24 hrs, and 48 hrs after surgery. Mean core (oesophageal) temperatures were recorded at the moment of anesthesia induction and after 30, 60, 90, and 120 min.

Concentrations of epinephrine and norepinephrine were measured by competitive ELISA tests (Labor Diagnostika Nord), while concentrations of cortisol, prolactin, and testosterone were measured by the ECLIA method (Elecsys® 2010, Roche).

Statistical analysis

After being tested for normality (by Kolmogorov-Smirnov test), data were presented as mean ± standard deviation (SD) for continuous data, or median followed by interquartile range. The significance of differences between groups and between time points was tested using the *t*-test or Mann-Whitney *U* test (comparison of two groups), ANOVA of Kruskal-Wallis test, *post hoc* Mann-Whitney or Tukey test (multigroup comparison). The statistical significance was accepted at $p < 0.05$. Complete statistical analysis was performed using SPSS 18 package (Chicago, USA). The sample size was calculated using a test power of 0.8 and a Type I (alpha) error of 0.05, which revealed that a sample size of 15 per group could detect the statistically significant differences between independent groups (GPower 3.1).

Results

The baseline characteristics of the patients in all groups, as well as the environmental conditions in the operation theatre, are presented in Table 1. There were no significant differences between the groups.

There was a statistically significant difference between average intraoperative esophageal temperatures regarding time points, and between groups. In the W and A+W groups, the temperatures did not significantly differ between time points but constantly decreased in the C and A groups, with a statistically significant difference between the anesthesia induction and the 120th min (35.61 ± 0.42 vs. 33.86 ± 0.71 °C; $p < 0.000$ and 35.81 ± 0.54 vs. 34.45 ± 0.41 °C; $p < 0.000$, respectively) (Figure 1).

Temperatures in these two groups have had slower recovery after surgery, i.e., postoperative esophageal temperatures were significantly lower compared to the other two groups in all time points (Figure 2). At the 90th min average temperatures were 34.38 ± 1.17 (C) and 35.41 ± 0.79 °C (A) compared to 36.07 ± 0.86 (W) and 36.4 ± 0.66 °C (A+W); $p < 0.000$.

Average concentrations in all groups at four-time points are presented in Table 2.

Statistical analysis by Wilcoxon Signed Ranks revealed a highly significant difference between epinephrine concentrations pre- and postoperatively in all 4 groups: (Z = -3.408, $p < 0.01$ in the C group; Z = -3.181, $p < 0.01$ in the A group; Z = -3.351, $p < 0.01$ in the W group, and Z = -3.408, $p < 0.01$ in the A+W group). Despite the highest postoperative values recorded in the control group, the differences were not statistically significant (Table 2).

Table 1

Characteristics of patients and environments

Characteristic	Control group (C)	Amino acid group (A)	Warming mattress group (W)	Combined warming group (A+W)
Age (years)	65.19 ± 4.89	63.89 ± 4.34	63.25 ± 5.8	62.23 ± 3.87
Males	60	40	53.33	46.66
Females	40	60	46.66	53.33
Body weight (kg)	74.28 ± 5.16	73.89 ± 5.65	72.9 ± 6.12	73.24 ± 5.87
Duration of anesthesia (min)	141.28 ± 16.13	139.55 ± 13.59	133.46 ± 12.02	137.21 ± 14.12
Temperature in operation theatre (ºC)	21.25 ± 1.52	21.22 ± 1.47	21.14 ± 1.64	21.18 ± 1.56
Relative humidity (%)	57.13 ± 6.28	56.35 ± 5.59	55.6 ± 5.55	56.25 ± 5.84
Wind speed (m/s)	0.21 ± 0.04	0.21 ± 0.02	0.22 ± 0.04	0.22 ± 0.02

Results are presented as mean ± standard deviation or percentage of patients.

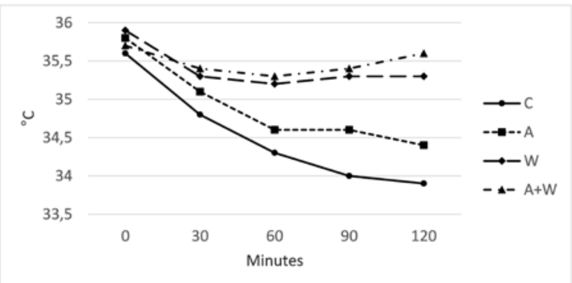

Fig. 1 – Intraoperative esophageal temperatures in all groups.
C – control group (non-warmed); W – group warmed with a forced-air mattress;
A – group warmed with an infusion of amino acids; A+W – combined warmed group.

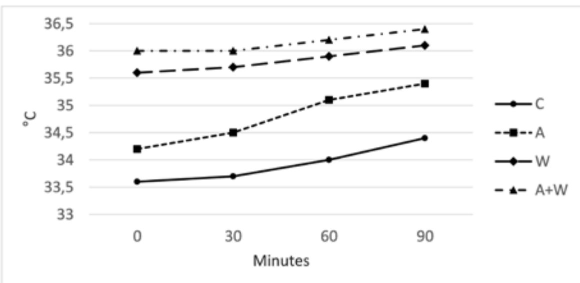

Fig. 2 – Postoperative esophageal temperatures in all groups.
C – control group (non-warmed); W – group warmed with a forced-air mattress;
A – group warmed with an infusion of amino acids; A+W – combined warmed group.

A similar trend was noticed in concentrations of norepinephrine (Table 2). Basic levels of norepinephrine were similar in all 4 groups, i.e., there were no statistically significant differences between groups. In all 4 groups, a highly significant increase was recorded in postoperative values compared to preoperative (Z = -3.181, $p < 0.01$ in the C group; Z = -2.556, $p < 0.01$ in the A group; Z = -3.237, $p < 0.01$ in the W group, and Z = -2.358, $p < 0.01$ in the A+W group). These values did not differ between groups.

Peak values of cortisol concentrations were recorded 120 min after surgery in all groups. After that, the values decreased toward basic levels in the following 2 days (Table 2). There was a highly significant difference between 4-time points (Wilks Lambda = 0.338; F = 35.323, Partial Eta Squared = 0.662; $p < 0.01$) and between 4 groups (F = 6.002, Partial Eta Squared = 0.243; $p < 0.01$).

Multiple comparison analyses (Tukey test) revealed a highly significant difference between internal warming (A group) compared to the C and W groups (Table 3).

Basic levels of prolactin showed no statistically significant differences between groups. Levels of prolactin were highest 120 minutes postoperatively in all groups (Table 2). There was a statistically significant difference between four-time points (Wilks Lambda = 0.604; F = 11.795, Partial Eta Squared = 0.396; $p < 0.01$) and between groups (F = 4.857, Partial Eta Squared = 0.206; $p < 0.01$). Multiple comparisons (Tukey test) revealed a statistically significant difference between the A group and all other groups ($p < 0.05$).

Concentrations of testosterone decreased in all groups during the surgical procedures and remained lower 24 and 48 hrs after surgery (Table 2). The difference was statistically significant in the W and A+W groups. Tukey test: in the W group: 90 min prior to surgery compared to 120 min after surgery, $p = 0.043$; 24 hrs after, $p = 0.016$; 48 hrs after, $p = 0.032$; in the A+W group: 90 min prior to surgery vs. 120 min after, $p = 0.013$; 24 hrs after, $p = 0.008$; 48 hrs after, $p = 0.022$. There was no significant difference between groups (F = 0.992; Partial Eta Squared = 0.051; $p = 0.403$).

Discussion

Intraoperative hypothermia is a multifactorial and complex condition. It is inadvertent and frequent. The induction and maintenance of general anesthesia change the normal protective response to hypothermia. Because of anesthesia-induced vasodilation and impairment of the normal thermoregulation (reduction of thermogenesis, both shivering and non-shivering), there is significant redistribution of heat from the core to the periphery [1]. Effector response to hypothermia is also altered [6]. Heat loss is influenced by environ-

Table 2

Concentrations of hormones at four-time points in all groups

Hormone	Group	Mean ± standard deviation			
		90 min before surgery	120 min after surgery	24 hrs after surgery	48 hrs after surgery
Epinephrine (pg/mL)	C	106.13 ± 89.63	777.07 ± 800 .08	-	-
	A	53.47 ± 52.022	388.27 ± 293.48	-	-
	W	79.60 ± 81.06	442.07 ± 517.83	-	-
	A+W	80.80 ± 60.99	664.33 ± 606.33	-	-
Norepinephrine (pg/mL)	C	580.53 ± 465.38	1349.67 ± 984.16	-	-
	A	588.73 ± 452 ± 93	1265.67 ± 949.13	-	-
	W	313.53 ± 357.68	800.53 ± 738.04	-	-
	A+W	318.80 ± 238.16	937.80 ± 1063.43	-	-
Cortisol (nmol/L)	C	533.57 ± 199.92	1211.23 ± 373.98	654.29 ± 221.49	494.71 ± 165 ± 39
	A	408.98 ± 201.88	542.98 ± 340.96	584.15 ± 339.08	486.57 ± 418 ± 59
	W	573.22 ± 188.70	1351.59 ± 482.12	643.31 ± 211.01	514.16 ± 183.28
	A+W	400.09 ± 191.49	803.64 ± 279.66	631.65 ± 399 ± 79	495.07 ± 373.74
Prolactin (µIU/mL)	C	226.98 ± 138.32	624.29 ± 417.18	230.51 ± 86.97	273.34 ± 140.11
	A	411.64 ± 224.59	1106.74 ± 922.42	707.51 ± 840.59	487.96 ± 280.82
	W	237.36 ± 166.69	638.37 ± 335.53	258.37 ± 172.69	315.56 ± 211.55
	A+W	295.72 ± 257.15	1162.44 ± 11.6359	363.26 ± 373.29	506.52 ± 479.99
Testosterone (nmol/L)	C	8.92 ± 7.16	6.38 ± 6.01	5.67 ± 4.27	5.74 ± 5.14
	A	6.31 ± 7.48	4.20 ± 4.92	5.27 ± 4.00	3.49 ± 3.18
	W	10.32 ± 8.29	6.41 ± 4.79	5.66 ± 4.19	5.33 ± 4.41
	A+W	11.67 ± 7.69	6.24 ± 4.04	6.75 ± 4.18	5.89 ± 3.86

C – Control group (non-warmed); W – Group warmed with a forced-air mattress; A – Group warmed with amino acids; A+W – Combined warmed group.

Table 3

Multiple comparisons of groups (Tukey test)

Group I	Group II	Mean difference (I-II)	*p*
A	C	-217.7777	< 0.01
	W	-264.8993	< 0.01
A+W	W	-187.9583	< 0.05

C – Control group (non-warmed); W – Group warmed with a forced-air mattress; A – Group warmed with amino acids; A+W – Combined warmed group.

mental conditions in the operating theatre. An essential factor in intraoperative heat loss is the surgical procedure itself. We enrolled patients who underwent large and long abdominal surgical procedures with exposed abdominal cavities. In this setting, hypothermia is a significant problem [6].

One of the endpoints of our study was to evaluate the efficacy of external warming, amino acid-induced endogenous thermogenesis, and their combination in patients undergoing major open abdominal surgical procedures. We have noted an increased interest in this topic in recent years. In our investigation, after the first 30 min of surgery, the lowest esophageal temperature was recorded in the C group. At this time point, the highest temperature was in the A+W group, and the same trend was sustained throughout the entire surgical procedure and up to 90 min after surgery.

Intraoperative hypothermia is defined as an esophageal temperature below 36 °C. After 30 min of surgery, the frequency of hypothermia was 100% in the group C and 93% in the groups A and W. Lowest frequency of hypothermia (80%) was in the group A+W. After 120 min of surgery, all patients in the groups C and A were hypothermic. The frequency of hypothermia in the group W was 86.6%. Again, the lowest frequency of hypothermia (66.6%) was in the A+W group.

In our study, it is evident that more than half of the patients remained hypothermic despite air warming mattress and/or amino acid infusion both 30 min and 120 min after anesthesia induction. That is in accordance with the results from a large retrospective study regarding intraoperative core temperature patterns in patients warmed with forced air [7]. The authors demonstrated that more than 60% of the patients were hypothermic 45 min after induction and that 20% continued being hypothermic for more than 120 min. Administration of iv nutrients, such as amino acids, has been investigated in normothermia maintenance settings due to endogenous metabolic heat production as well as the increase of whole-body heat content by 20% [8]. Salem et al. [9] investigated 42 cancer patients who underwent pelvic abdominal surgery, randomized to receive either amino acid infusion or warm Ringer solution infusion 2 hrs before anesthesia induction. Authors concluded that amino acid infusion before anesthesia and surgery restored core body temperature: in the first 120 min in this group, there was no hypothermia [9]. These results are at odds with ours regarding the A group: after 120 min, all patients were hypothermic. Different results are expected due to the difference in the study design – in our study, infusion started immediately after anesthesia induction while in the study by Salem et al. [9], infusion of the amino acid solution was completed two hrs before anesthesia.

Amino acids infusion might be intraoperatively beneficial for surgical patients because it can counteract the disadvantageous fasting metabolism; metabolic fate is two-fold: oxidation for energy production and/or building blocks for protein synthesis. In both cases, large amounts of energy are needed for amino acid metabolism and possibly heat production [10]. A recent systematic review and meta-analysis regarding perioperative amino acid infusion for preventing hypothermia demonstrated that, based on 626 participants from 14 randomized controlled trials, amino acid infusion led to a +0.46 °C increase in temperature. The authors concluded that this minor difference is of clinical significance and that this method of normothermia maintenance has a similar effect as conventional warming systems and may serve as a viable alternative [11].

In several studies, various methods of perioperative prewarming and warming were investigated in surgical procedures other than exclusively major open abdominal ones [12–14]. The authors concluded that active warming is more efficient than passive in hypothermia prevention. Yet, even with active warming, hypothermia persisted in some patients. The authors also emphasized that continued innovation in active warming technology and research in different methods of active warming is necessary. Given that, one would expect an investigation of various methods of intraoperative warming. Yet, interestingly, in the literature available to us, we did not find any studies regarding the combination of external warming and amino acid-induced endogenous thermogenesis in the prevention of inadvertent intraoperative hypothermia. One recent investigation included a combination of forced-air warming and warmed iv fluid consisting of lactated Ringer solution but not amino acids [1]. Our results showed that the mean core temperature was highest in the group A+W at the 120th min after anesthesia induction. At that time point, the lowest frequency of hypothermia was again in the group A+W. It would seem that combination of endogenous amino acid-induced thermogenesis and external warming mattress is most effective in preventing intraoperative hypothermia.

The primary aim of our study was to investigate stress hormone response in patients undergoing major surgery and the effects of various warming methods. Our results show a substantial increase in concentrations of catecholamines in the postoperative period in all groups. The highest values were recorded in non-warmed patients, but we found no significant difference compared to other groups. Moreover, despite the notably higher fundamental values in the groups C and A compared to the other two groups, these differences did not reach statistical significance. Frank et al. [15] indicated that a decrease in core temperature by 1.5 °C is related to higher epinephrine concentration in the early postoperative period. At the same time, maintenance of normothermia shows little effect on epinephrine and norepinephrine concentrations. Initial studies also failed in the attempt to relate the effects of intraoperative hypothermia to catecholamine response, probably due to an insufficient number of participants, confounding influence of age, lack of randomization, and lack of standardized postoperative analgesia [16, 17]. Other published results also reported that mild intraoperative hypothermia does not have an important effect on stress hormone concentrations in hypothermic patients [18, 19]. In the same study, authors simultaneously estimated cortisol response and did not find any intraoperative increase in its concentrations. Frank et al. [15] found that postoperative cortisol concentrations were much higher in patients who underwent general anesthesia compared to patients exposed to combined or regional anesthesia, with the conclusion that cortisol response is determined by anesthesiology technics rather than hypothermia. In our study, peak values of cortisol levels were achieved in all groups 120 min after surgery, with statistically significant differences regarding the warming method. In the group with simulated endogenous thermogenesis by intravenous administration of the amino acid solution, the lowest changes in cortisol levels were recorded intraoperatively and postoperatively compared to other groups. In all groups, cortisol concentrations tend to normalize in the following 48 hrs.

Along with other stress hormones, surgical stress and intraoperative hypothermia also induce prolactin secretion [20], probably *via* a central dopaminergic mechanism. An increase in prolactin concentration in all four groups in our study, with peak values measured 120 min after surgery, presented the statistically significant difference between groups warmed with amino acids and the combination of amino acids and forced-air mattress compared to the other two groups, which supported the conclusion that amino acids were responsible for the observed difference. Interestingly, we recorded somewhat higher basic levels of prolactin in the A group compared to the other three groups, but the difference was not statistically significant. After 48 hrs, prolactin concentrations decreased toward baseline levels, which is in agreement with recently published results [20].

Finally, analyzed testosterone response presented with a decrease in concentrations after surgery in all groups, and lower levels were sustained throughout the entire observation, i.e., the following 48 hrs. The differences between baseline levels and postoperative measurements were statistically significant in the W and A+W groups, but there was no difference between groups at any time point. Lindh et al. [20] recorded maintenance of low concentration of testosterone up to the 16th postoperative day, with inevitable impairment of anabolic processes necessary for recovery. According to our findings, as well as results reported in other studies, we may notice that major surgical trauma and perioperative hypothermia impose rapid, intensive, and long-lasting effects on gonadal activity (reflected by decreased testosterone levels), while the effect on suprarenal activity is rather mild.

There are several limitations in our study: although the sample size was sufficient for correct statistical analysis, reported patterns and trends in stress hormone profiles and methods of hypothermia should be confirmed in a larger population. In addition, our results are obtained in patients undergoing specific surgical intervention in GBA; hence further investigations need to be conducted in other types of surgery and other types of anesthesia.

Conclusion

Prevention of intraoperative hypothermia is of major importance in reducing complications associated with avoidable hypothermia in surgical patients. This study demonstrates the effects of intraoperative hypothermia and three warming methods on stress hormone response in patients who underwent major open abdominal surgical procedures. Both external and internal warming methods were effective in attenuating intraoperative and postoperative hypothermia, and the most effective was forced-air mattresses *per se* or in combination with internal warming. A comparison of catecholamine concentrations measured 90 min before and 120 min after surgical procedures revealed a significant increase during surgery, with the highest values recorded in the non-warmed group. Concentrations of cortisol and prolactin also showed a significant increase at the same time point, with a tendency to normalize after 48 hrs. On the contrary, testosterone concentrations showed a decrease after 120 min without normalization throughout the entire period of observation. Except for testosterone, changes in all stress hormones were attenuated in warmed groups compared to controls, and internal warming (amino acid solution) with or without forced-air mattresses was the most effective. Regarding both features of surgical stress investigated in this study (hypothermia and stress hormone response), the combination of endogenous amino acid-induced thermogenesis and external air warming mattress is most effective in its prevention.

R E F E R E N C E S

1. *Jun JH, Chung MH, Jun IL, Kim Y, Kim H, Kim JH*, et al. Efficacy of forced-air warming and warmed intravenous fluid for prevention of hypothermia and shivering during cesarean delivery under spinal anesthesia Eur J Anaesthesiol 2019; 36(6): 442–8.
2. *Zeba S, Surbatovic M, Jevtic M, Filipovic N, Popovic N, Radakovic S*, et al. Influence of perioperative administration of amino acids on thermoregulation response in patients underwent colorectal surgical procedures. Vojnosanit Pregl 2007; 64(6): 421–4. (Serbian)
3. *Zeba S, Surbatovic M, Marjanovic M, Jevdjic J, Hajdukovic Z, Karkalic R*, et al. Efficacy of external warming in attenuation of hypothermia in surgical patients. Vojnosanit Pregl 2016; 73(6): 566–71.
4. *Goldestein DS*. Catecholamines and stress. Endocr Regul 2003; 37(2): 69–80.
5. *Nicholson G, Hall GM*. Stress response during surgery. In: Kumar CM Bellamy M, editors. Gastrointestinal and colorectal anaesthesia. New York: Informa Healthcare; 2007. p. 33–44.
6. *Matika R, Ibrahim M, Patwardhan A*. The importance of body temperature: An anesthesiologist's perspective. Temperature (Austin) 2016; 4(1): 9–12.
7. *Sun Z, Honar H, Sessler DI, Dalton JE, Yzng D, Panjasawatwong K*, et al. Introperative core temperature patterns, trasfusion requirement and hospital duration in patients warmed with forced air. Anesthesiology 2015; 122(2): 276–85.
8. *McSwain JR, Yared M, Doty JW, Wilson SH*. Perioperative hypothermia: causes, consequences and treatment. World J Anesthesiol 2015; 4(3): 58–65.
9. *Salem WT, Eldin Helaly MK, Hassan MM, Radwan NH, Samy SF*. Effect of perioperative amino acid infusion on intraoperative hypothermia and postoperative shivering during pelvi-abdominal surgery in cancer patients. Med J Cairo Univ 2017; 85(7): 2583–9.
10. *Yokoyama T, Yamaoka I, Hitosugi T, Sellden E*. Amino acids during perioperative period. Open J Anesthesiol 2017; 7(9): 287–95.
11. *Aoki J, Aoshima Y, Atsumi K, Kaminaka R, Nakau R, Yanagida K*, et al. Perioperative amino acid infusion for preventing hypothermia and aimproving clinical outcomes during surgery under general anesthesia. A systematic review and meta-analysis. Anesth Analg 2017; 125(3): 793–802.

12. *Torrosian A, Van Gerven E, Geertsen K, Horn B, Van de Velde M, Reader J.* Active perioperative patient warming using a self-warming blanket BARRIER Easy Warm is superior to passive thermal insulation: a multinational, multicenter, randomized trial. J Clin Anesth 2016; 34: 547–54.
13. *de Bernardis RC, Siaulys MM, Vieira JE, Mathias LA.* Perioperative warming with a thermal gown prevents maternal temperature loss during elective cesarean section. A randomized clinical trial. Braz J Anesthesiol 2016; 66(5): 451–5.
14. *Tyvold SS.* Preventing hypothermia in outpatient plastic surgery by self-warming or forced-air-warming blanket: A randomized controlled trial. Eur J Anaesthesiol 2019; 36(11): 843–50.
15. *Frank SM, Higgins MS, Breslow MJ, Fleisher LA, Gorman RB, Sitzman JV,* et al. The catecholamine, cortisol and hemodynamic responses to mild perioperative hypothermia: a randomized clinical trial. Anesthesiology 1995; 82(1): 83–93.
16. *Breslow MJ, Parker SD, Frank SM, Norris EJ, Yates H, Raff H*, et al. The PIRAT Study Group: Determination of catecholamine and cortisol response to lower extremity revascularization. Anesthesiology 1993; 79(6): 1202–9.
17. *Holcher C, van Aalten L, Sutherland C.* Anesthesia generates neuronal insulin resistance by inducing hypothermia. BMC Neurosci 2008; 9: 100.
18. *Yi JW, Choi YK.* The hemodynamic changes and stress hormone responses to mild intraoperative hypothermia during intravenous anesthesia (in neurosurgical patients). Korean J Anesthesiol 2003; 45(6): 702–9.
19. *Chi OZ, Choi JK, Lee DI, Kim YS, Lee I.* Intraoperative mild hypothermia does not increase the plasma concentration of stress hormones during neurosurgery. Can J Anaesth 2001; 48(8): 815–8.
20. *Lindh A, Carlstrom K, Eklund J, Wilking N.* Serum steroids and prolactin during and after major surgical trauma. Acta Anaesthesiol Scand 1992; 36(2): 119–24.

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