Role of amino acids infusion in prevention of anesthesia induced hypothermia and postoperative shivering

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Background: *Hypothermia results from heat loss exceeding heat production. Core temperature during this phase therefore depends on system heat balance. Because anesthetics profoundly impair thermoregulatory control factors that increase thermogenesis or reduce loss of heat to the environment, they moderate the rate at which intraoperative hypothermia develops. We evaluate the ability of amino acids infusion to prevent anesthesia induced hypothermia and postoperative shivering in patients receiving anesthesia.* ***Methods***: *80 patients, with ASA physical status I & II undergoing abdominal surgeries or orthopedic who were randomly allocated into 2 groups, each one subdivided into two groups: Group I: (n=40) under general anesthesia: subdivided into Group Ia: (n=20) received amino acids intravenously infusion. Group Ib: (n=20) received corresponding volumes of nutrient-free saline solution intravenously infused. Group II: (n=40) under spinal anesthesia Subdivided into two groups: Group IIa: (n=20) received amino acids intravenously infusion. Group IIb (control group): (n=20) received corresponding volumes of nutrient-free saline solution intravenously infused. Core body temperature was continuously monitored via rectal thermistor probe, Surface (skin) temperature was monitored; Arterial blood gases and pH analysis, serum cortical, serum glucose and serum lactate was done every 30 min. All patients were assessed every 30 min in the first 2 hours c Pain at rest was scored on the visual analogue scale (VAS).* ***Results***: *The study revealed that preoperative amino acids infusion decreased significantly the magnitude of anesthesia induced hypothermia and enhanced the rate of recovery from it. The rate of postoperative shivering was significantly reducing in amino acids treated groups. Hypothermia induced postoperative adverse effects as hypertension and shivering associated increased postoperative pain and hypoventilation were significantly reduced by the infusion of amino acids .Arterial blood gases, pH analysis, serum glucose, serum cortical and serum lactate were nearly comparable in the studied groups, suggesting that the amino acids infusion did not produce uncompensated metabolic or respiratory stress for patients receiving it.* ***Conclusion***: *It can be concluded that amino acids infusions restore core body temperature and almost eliminated postoperative shivering.*

Introduction:

The combination of anesthetic-induced impairment of thermoregulatory control and exposure to a cool operating room environment renders most surgical patients to be

hypothermic. Intraoperative core temperature depends on both distribution of heat within the body and on systemic heat balance [1]. Subsequently, however, hypothermia results from heat loss exceeding heat production [2]. factors that increase thermogenesis or reduce loss of heat to the environment moderates the rate at which intraoperative hypothermia develops [3].

Several prospective, randomized trials have demonstrated various hypothermia-induced complications such as surgical wound infection, prolonged duration of hospitalization, intraoperative blood loss, myocardial ischemia, ventricular dysrhythmia, postoperative shivering, prolonged postanesthetic recovery duration, increased O_2 consumption, metabolic acidosis and thermal discomfort.[4]

Patients report that shivering is remarkably uncomfortable, and some even find the accompanying cold sensation worse than surgical pain. Moreover, shivering per se may aggravate postoperative pain simply by stretching surgical incisions. Shivering also occasionally impedes monitoring techniques, increases intraocular and intracranial pressures, and is especially disturbing to mothers during labor and delivery. [5]

It is well known from earlier studies that in the anesthetized state, administration of nutrients, especially protein and amino acid mixtures, stimulates resting energy expenditure. Moreover, approximately 60% of the extra heat produced in response to amino acid administration accumulates, thus increasing the temperature of mixed venous blood.[6]

The balance between heat production and heat loss determines the body temperature. In the human body, heat is produced by muscular exercise, assimilation of food, and all the vital processes that contribute to the basal metabolic rate. It is lost from the body by radiation, conduction, and vaporization of water in the respiratory passages and from the skin. Small amounts of heat are also removed in the urine and feces. Because the speed of chemical reactions varies with the temperature and because the enzyme systems of the body have narrow temperature ranges in which their function is optimal, normal body function depends upon a relatively constant body temperature.[7]

Thermoregulation is similar to many other physiologic control systems in that the brain uses negative and positive feedbacks to minimize perturbations from preset, "normal" values. Thermoregulation is now known to be based on multiple, redundant signals from nearly every type of tissue. The processing of thermoregulatory information occurs in three phases: afferent thermal sensing, central regulation, and efferent responses [5] Temperature information is obtained from thermally sensitive cells throughout the body. Cold-sensitive cells are anatomically and physiologically distinct from those that detect warmth.

Temperature is regulated by central structures (primarily the hypothalamus) that compare integrated thermal inputs from the skin surface, neuraxis, and deep tissues with threshold temperatures for each thermoregulatory response.[5]

The body responds to thermal perturbations (body temperatures differing from the

appropriate threshold) by activating effector mechanisms that increase metabolic heat production or alter environmental heat loss. In general, energy-efficient effectors such as vasoconstriction are maximized before metabolically costly responses such as shivering are initiated.[8]

Behavioral regulation is not relevant during general anesthesia because patients are unconscious and frequently paralyzed. Anesthetic induced impairment has a specific form: warm-response thresholds are elevated slightly, whereas cold-response thresholds are markedly reduced. Consequently, the interthreshold range is increased from its normal values near 0.2°C to about 2 to 4°C [9]

Core temperature, though, poorly represents mean body temperature because peripheral tissues are typically 2–4°C cooler than the trunk and the head. This normal core-to-peripheral tissue temperature gradient is maintained by tonic thermoregulatory vasoconstriction of arterio-venous shunts in the fingers and toes [10]

Induction of general anesthesia promotes vasodilation via two mechanisms: This internal redistribution of body heat decreases core temperature and proportionately increases temperature of peripheral tissues; it does not, however, represent any net exchange of heat to the environment, and body heat content remains constant.[11] The second portion of the hypothermia curve is a relatively slow, linear decrease in core temperature. It results simply from heat loss exceeding metabolic heat production. Metabolic rate is reduced by 15–40% during general anesthesia[6]. Cutaneous heat loss is mediated by the same four fundamental mechanisms that modulate heat transfer between any two substances: radiation, conduction, convection, and evaporation.

The final phase of the typical intra-operative hypothermia curve is a core temperature plateau that usually develops after 2–4 h of anesthesia and surgery. It is characterized by a core temperature that remains constant, even during prolonged surgery. The core temperature plateau is sometimes passive, and sometimes actively maintained[11]. A passive plateau results when metabolic heat production equals heat loss, without activating thermoregulatory defenses. However, several factors complicate the situation during anesthesia and surgery: Anesthesia significantly decreases metabolic heat production[10]. Heat loss may be abnormally high because of a relatively cool operating room environment, administration of cool intravenous and irrigating fluids and evaporative and radiative losses from within surgical incisions[12].

Autonomic thermoregulation is impaired during regional anesthesia, and the result is typically intraoperative core hypothermia. Interestingly, this hypothermia is often not consciously perceived by patients, but it nonetheless triggers shivering. The result is frequently a potentially dangerous clinical paradox: a shivering patient who denies feeling cold.

Epidural anesthesia[13] and spinal anesthesia each decrease the thresholds triggering

vasoconstriction and shivering (above the level of the block) about 0.6°C Regional anesthesia blocks all thermal input from blocked regions, which in the typical case is primarily cold information. The brain may then interpret decreased cold information as relative leg warming. This appears to be an unconscious process because perceived temperature does not increase[14].

The major consequences of mild perioperative hypothermia include morbid myocardial outcomes, augmented blood loss and allogeneic surgical wound infections, and a 20% prolongation of hospitalization. Other important consequences include delayed postanesthetic recovery, protein wasting, reduced drug metabolism, and shivering. Blood loss increases roughly 0.5 units for each degree Celsius decrease in core temperature. A recent meta-analysis confirms that even very mild hypothermia increases both[15].

Shivering-like tremor occurs in approximately 40% of patients recovering from anesthesia and is preceded by core hypothermia and peripheral vasoconstriction, indicating that it is thermoregulatory. Shivering also occasionally impedes monitoring techniques[16], increases intraocular and intracranial pressures.[5]

Shivering can double or even triple oxygen consumption and carbon dioxide production, although the increases are typically much smaller. These large increases in metabolic requirement might predispose to difficulties for patients with existing intrapulmonary shunts, fixed cardiac output, or limited respiratory reserve. However, shivering is rarely associated with clinically important hypoxemia because hypoxia itself inhibits this response [5]. Shivering-like tremor in volunteers given neuraxial anesthesia is always preceded by core hypothermia and vasoconstriction (above the level of the block)[17]. Spinal thermal receptors have been detected in every mammal and bird tested. Experimental stimulation of these receptors reliably produces shivering in animals. Stimulation of these putative receptors by injection of an epidural anesthetic in humans could theoretically initiate thermoregulatory responses, including shivering[18].

The risk of shivering during neuraxial anesthesia is markedly diminished by maintaining strict normothermia. However, there is a distinct incidence of low-intensity, shivering-like tremor that occurs in normothermic patients and is not thermoregulatory[19]. The cause of this muscular activity remains unknown, but it is associated with pain and may thus result from activation of the sympathetic nervous system.

Patients and Methods:

Eighty healthy, adult patients, of class ASA I and II, from both sexes, and undergoing abdominal surgeries or orthopedic (total hip or knee) lasting for more than two hours and less than four hours. This study was done in Benha University hospitals after approval of the local Ethical Committee and obtaining an informed consent from each patient.

Patients included in the study were assigned randomly into one of the two following groups:

Group I: ***(n=40)*** **(under general anesthesia)** Subdivided into:

Group Ia: this group was composed of 20 patients who received amino acids intravenously infusion at a rate of 250ml/hour (corresponding to 260kJ/h) for one hour before anesthesia and continuing throughout the first hour of anesthesia.

Group Ib (control group): this group was composed of 20 patients who received corresponding volumes of nutrient-free saline solution intravenously infused for one hour before anesthesia and the first hour intra-operatively.

Group II: ***(n=40)*** **(under spinal anesthesia)** Subdivided into:

Group IIa: this group was composed of 20 patients who received amino acids intravenously infusion at the same rate as in group Ia, for one hour before the inducion of spinal anesthesia and continuing throughout the first hour of anesthesia.

Group IIb (control group): this group was composed of 20 patients who received corresponding volumes of nutrient-free saline solution intravenously infused for one hour before anesthesia and the first hour intra-operatively.

All patients received premedication of midazolam 1-3mg i.v. given one hour before induction of anesthesia in all groups. Operating room temperature was maintained at 24°C, no warming devices were being applied except for ordinary surgical draping and all the infused fluids were kept at room temperature.

Anesthetic protocol:

In group I the general anesthesia was induced with sleep dose of thiopental sodium (3-6 mg/kg), and maintained with isoflurane. Tracheal Intubation was performed after an i.v. bolus dose of atracurium (0.5mg/kg) & fentanyl 2µg/kg was given, and when the patient was fully relaxed. Mechanical ventilation was started and was adjusted to maintain end-tidal CO_2 tension between 34-36 mmHg. Anesthesia was maintained by 0.5-1% Isoflurane, with muscle relaxation maintained by atracurium 0.15mg/kg whenever needed as indicated by nerve stimulator. After the end of surgery and recovery of neuromuscular blockade was indicated by nerve stimulator, 2.5mg neostigmine and 1mg atropine was administered intravenously for the complete reversal of the neuromuscular blockade. Extubation was performed when the patient met the standard extubation criteria (regular spontaneous breathing, end tidal carbon dioxide <45 mmHg and SPO_2 > 95% on room air), then was transferred to the post-anesthetic care unit (PACU) in which he/she was inspiring humid 40% oxygen in air.

In group II the spinal anesthesia will be induced with 25 µg fentanyl added to (2.5-3ml) heavy marcaine 0.5%.

Monitoring

Routine vital signs monitoring of heart rate, blood pressure, oxygen saturation, end tidal CO_2 and ECG was continuously displayed.

Temperature monitoring: Core body temperature was continuously monitored via rectal thermistor probe which was inserted 10-15 cm, to assure the detection of core temperature.

Surface (skin) temperature was monitored with another probe fixed on the skin of the lumbar region.

Monitoring was started just before amino acids infusion (base line), and then continuously performed for six hours started just before the induction of anesthesia.

Arterial blood gases and pH analysis was done every 30 min. starting just before the starting of amino acids infusion till six hours from the induction of anesthesia. serum cortisol, serum glucose and serum lactate were measured just before starting of amino acids infusion, before induction of anesthesia, immediately postoperative and 2 hours postoperatively. All patients were assessed every 30 min in the first 2 hours postoperatively for the presence of pain and shivering. Pain at rest was scored on the visual analogue scale (VAS) which consisted of an unmarked 100 mm line, with 0 mm representing no pain and 100 mm representing the worst imaginable pain. If VAS was more than 40mm, 75mg diclofenac Na i.m. injection was given.

Shivering was assessed using the following score:

0	No shivering
1	palpable mandible vibration or ECG artifact
2	visible fasciculations of head and neck
3	visible fasciculations of pectoral muscles or trunk
4	generalized shivering of entire body

(Holtzclaw, 1986) [20]

30mg mepridine i.v. injection was given if shivering score was more than 2.

Results:

As regard age, weight, height and duration of anesthesia. The four studied groups have showed comparable and ASA classification distributions among their individuals Table (1).

Table (1): Demographic & operative characteristics among the four study groups

Time Interval	Group Ia	Group Ib	Group IIa	Group IIb	*P* Value
Age (yrs)	34.3±10.4	39.6±15.8	40.6±13.5	31.9±11.2	0.107
Sex (M:F)	12 (60%) 8 (40%)	7 (35%) 13 (65%)	14 (70%) 6 (30%)	10 (50%) 10 (50%)	0.193
Weight (kg)	78.2±13.9	73.0±16.5	69.8±14.7	75.1±18.2	0.404
Height (cm)	163.8±17.5	160.5±15.3	168.1±19.9	162.9±20.7	0.624
ASA Status (I:II)	5 (25%) 15 (75%)	13(65%) 7 (35%)	8 (40%) 12 (60%)	7 (35%) 13 (65%)	0.087
Surgical Time(min)	140.6±35.7	135.8±33.2	155.1±27.4	150.7±41.9	0.282
Surgical Type: ▪ Abdominoplasty ▪ Hysterectomy ▪ Abdominoperineal resection ▪ Colectomy ▪ Orthopedic (total hip or knee)	 3 (15%) 4 (20%) 2 (10%) 5 (25%) 6 (30%)	 5 (25%) 6 (30%) 4 (20%) 3 (15%) 2 (10%)	 4 (20%) 5 (25%) 4 (20%) 2 (10%) 5 (25%)	 2 (10%) 4 (20%) 3 (15%) 4 (20%) 7 (35%)	0.852

Values are expressed as mean ± SD.

No significant differences between groups comparison (***P*** Value > 0.05)

There was a statistically significant difference between groups as regard MAP values. This

difference was found to be between the control groups and amino acid treated groups .This difference was observed mainly in the early postoperative period during which the control groups showed statistically significant higher MAP than the other groups. Gradual decrease of MAP was then observed till it approached its baseline value at the end of the study period. The four groups showed the same pattern of MAP changes during the preoperative and intra-operative periods which were manifested by minimal gradual decrease in the mean values; one hour from the induction of anesthesia. But no significant difference between the studied groups during preoperative, intra-operative or postoperative as regard to heart rate.

Rectal temperature was elevated slightly in the amino acids treated groups (Ia group Ib) just before induction of anesthesia, while it was nearly the same in the control groups. The four groups showed the usual pattern of anesthesia–induced hypothermia during the intra-operative period, but it was less profound in group Ia and group IIa as indicated by statistically significant. During the postoperative period, group Ia and group IIa showed significantly higher rectal temperature than the other two groups. The four groups gradually approached the baseline normal temperature at the end of the study period (table 2).

Table (2): Mean perioperative rectal temperature changes among the four study groups

Time Interval	Group Ia	Group Ib	*P* Value	Group IIa	Group IIb	*P* Value
Baseline	36.97±0.24	36.95±0.26	0.802	37.0±0.24	36.9±0.32	0.271
0 hrs	36.95±0.55	36.60±0.34	0.02*	36.90±0.26	36.7±0.28	0.025*
0.5 hrs	37.10±0.15	36.95±0.26	0.031*	36.5±0.35	36.1±0.57	0.011*
1 hrs	36.36±0.25	36.16±0.22	0.011*	36.2±0.57	35.8±0.41	0.015*
1.5 hrs	36.10±0.31	35.90±0.17	0.016*	35.9±0.62	35.5±0.44	0.024*
2 hrs	35.88±0.44	35.50±0.33	0.005*	35.5±0.33	35.2±0.41	0.015*
2.5 hrs	35.75±0.31	35.42±0.47	0.013*	35.5±0.65	35.1±0.43	0.027*
3 hrs	35.81±0.35	35.38±0.43	0.001*	35.4±0.49	35.1±0.39	0.039*
3.5 hrs	35.84±0.44	35.30±0.52	0.001*	35.6±0.31	35.2±0.42	0.001*
4 hrs	36.14±0.57	35.6±0.47	0.002*	35.9±0.27	35.7±0.38	0.007*
4.5 hrs	36.33±0.66	35.77±0.54	0.006*	36.4±0.28	36.1±0.35	0.005*
5 hrs	36.55±0.45	36.06±0.51	0.003*	36.67±0.42	36.3±0.33	0.0004*
5.5 hrs	36.78±0.49	36.38±0.44	0.010*	36.64±0.29	36.4±0.33	0.019*
6 hrs	36.91±0.50	36.65±0.4	0.077	36.7±0.52	36.6±0.62	0.584

Values are expressed as mean ± SD.
No significant differences between groups comparison (***P*** Value > 0.05)
* = significant differences between group comparison (***P*** Value < 0.05).

As shown in table 3, rectal–to–skin temperature gradient was comparable in the groups throughout the studying period. Its mean baseline value was about 4.4^{o}C then a significant reduction was observed with mean value of about 2.2^{o}C that continued for one hour then a progressive significant increase was noticed till it reached a maximum mean value of 7.8^{o}C. During the postoperative period, the core–to–skin difference was gradually decreased till its normal, baseline values.

Table (3): Mean perioperative rectal - skin temperature gradient changes among the four study groups

Time Interval	Group Ia	Group Ib	*P* Value	Group IIa	Group IIb	*P* Value
Baseline	4.41±0.45	4.38±0.57	0.854	4.47±0.63	4.38±0.57	0.638
0 hrs	4.35±0.52	4.41±0.63	0.744	4.45±0.59	4.39±0.60	0.752
0.5 hrs	2.19±1.1	2.43±1.28	0.529	2.26±1.25	2.23±1.17	0.938
1 hrs	2.0±1.04	2.39±1.22	0.283	2.04±1.12	2.12±1.22	0.830
1.5 hrs	1.92±1.3	2.66±1.4	0.133	1.95±0.89	2.82±1.18	0.295
2 hrs	3.2±0.88	3.91±0.99	0.402	4.25±1.06	3.13±1.16	0.556
2.5 hrs	5.0±1.3	5.98±1.30	0.5	5.53±1.18	4.7±1.22	0.530
3 hrs	7.79±0.97	7.15±0.88	0.411	7.72±1.43	6.68±1.39	0.475
3.5 hrs	7.01±1.31	7.29±1.59	0.547	7.03±1.35	7.29±1.59	0.580
4 hrs	6.26±1.42	6.39±1.61	0.788	6.28±1.47	6.39±1.61	0.823
4.5 hrs	5.62±1.44	5.67±1.52	0.916	5.64±1.49	5.67±1.52	0.553
5 hrs	5.36±1.47	5.29±1.36	0.877	5.37±1.48	5.36±1.47	0.713
5.5 hrs	5.07±1.49	5.2±1.39	0.777	5.08±1.51	5.2±1.39	0.795
6 hrs	4.77±1.49	4.92±1.35	0.740	4.78±1.51	4.92±1.35	0.759

Values are expressed as mean ± SD.
No significant differences between groups comparison (***P*** Value > 0.05)
* = significant differences between group comparison (***P*** Value < 0.05).

pH was very slowly decreased during the intra-operative period but wasn't statistically significant differences between the groups except lately, 3.5– 4 hours from the induction of anesthesia there was statistically significant differences between the group Ia and group Ib; and also between group IIa and group IIb. Shortly, pH was returned back to its baseline value during the early postoperative period (within 2 hours).

As regarded to S.HCO3 levels and SPO2 there were no statistically significant differences between the four groups pre-operatively and intra-operatively and post-operatively.

Before induction of anesthesia, PaCO2 was slightly, but significantly, increased in group Ia and group IIa while maintained nearly constant in the control groups. There was no statistically significant difference between groups during the intra-operative period. Postoperatively, PaCO2 was slightly significant higher especially in the control group was gradually decreased to be comparable with its baseline value at the end of the study period.

Serum glucose levels were comparable between the four groups. There were no statistically significant differences between the groups pre-operatively, intra-operatively and post-operatively, but there was progressive increase in these levels to reach the maximum value immediately postoperatively. Two hours postoperatively, serum glucose levels started to decrease, but didn't reach the baseline value. Also the same pattern occur in serum cortisol levels were comparable between the four groups.

Lactate level was significantly higher in the control group than the other groups. This difference was observed in the postoperative period during which serum lactate level increased significantly in the four groups particularly in the control group, then rapidly returned back toward its baseline value after two hours postoperatively.

Postoperative shivering was significantly more frequent and more intense in the control group

than in the other two groups during the first hour postoperatively figure (1).

As shown in figure 2, postoperative pain at rest as indicated by VAS was significantly lower in the amino acids treated groups than in the control groups. The four groups showed significant decrease in the VAS values especially after the first hour postoperatively.

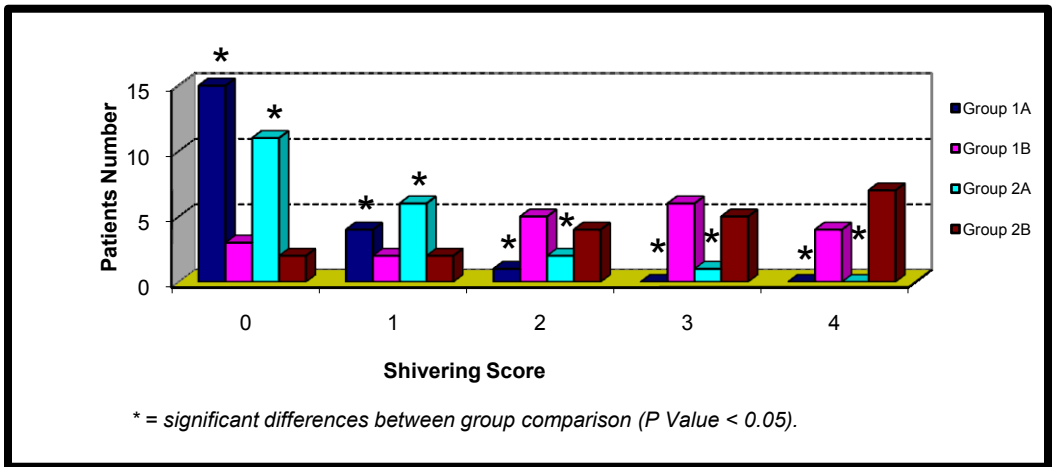

Figure (1): Postoperative shivering assessment among the four study groups

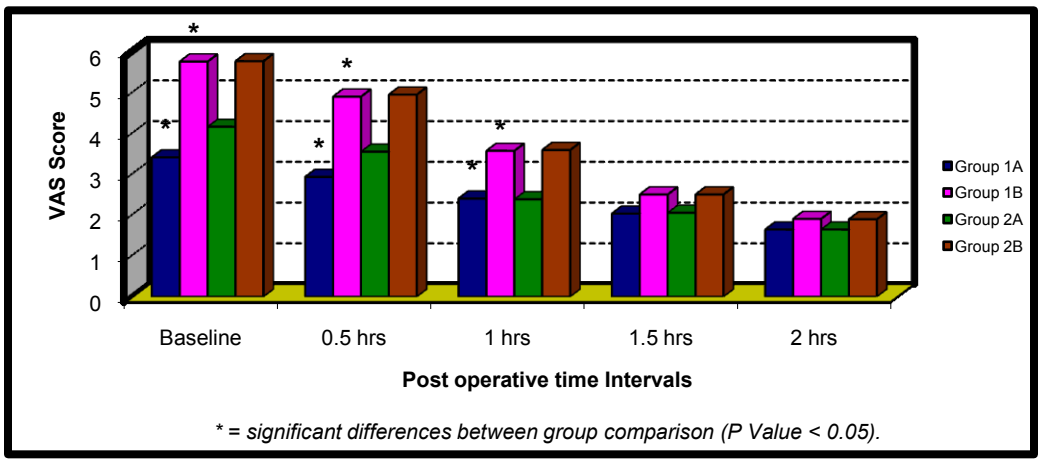

Figure (2): Postoperative visual analogue pain scores among the study groups

Discussion:

During anesthesia, there is a marked decrease in energy expenditure heat generation. In addition, central thermoregulatory function is impaired, delaying hypothermia defense mechanisms [21]. Many warming devices are in use to prevent heat loss, but little attention has been paid to stimulate the body's own heat generation[22]. During anesthesia, central thermosensors are silenced and hence, amino acid thermogenesis is exaggerated. The amino acid-induced heat generation during anesthesia predominantly occurs in extra-splanchnic tissues, most probably in skeletal muscle Amino acids infusion not only increases the metabolic rate and the resting core temperature but also increases the set point for all thermoregulatory autonomic responses [23].

In present study, the rectal temperature was increased after amino acids infusion in group Ia and group IIa before onset of anesthesia. This is constant with the study conducted in 2004 by Nakajima et al. which showed that amino acids infusion for 150min in nine male volunteers had increased their resting core temperature by 0.3±0.1 ^{o}C (mean±SD). [23]

Then rectal temperature was following the usual pattern of anesthesia–induced hypothermia, it was markedly decreased immediately after induction and during the first hour of anesthesia. This reduction was observed by the same rate in the four studied groups of the present study with simultaneous rapid reduction in the core–to–peripheral temperature gradient (from about 4.4^{o}C before induction of anesthesia to about 2.2^{o}C after one hour from its induction) suggesting that the amino acids infusion did not affect the rate of initial reduction of temperature due to redistribution of body heat after induction of anesthesia [24].

However, the rate of temperature reduction was progressively decreased after this first hour. Furthermore, the magnitude of this reduction was different in the four groups being less in the amino acids treated groups as indicated by the statistically significant difference than the control groups. This was most probably due to the increased metabolic rate enhanced by the infused amino acids. This increase compensates for the heat loss to the environment which distinguishes this period [25]. Postoperatively, the recovery from hypothermia was significantly faster in the amino acids treated groups than in the control group.

These findings are supported by many prospective randomized studies. In 1996, Sellden et al showed that preoperative infusion of amino acids in 16 female patients underwent hysterectomy and sex healthy women elevated significantly their mean rectal temperature by more than 0.2^{o}C per hour before induction of anesthesia as compared with infusion of nutrient free saline in another 8 patients (the control group). After induction of anesthesia, they reported immediate temperature reductions in all patients by nearly the same degree however; during the entire period of anesthesia and surgery, the decrease in temperature was significantly greater in the control group than in the amino acid treated groups [24]**.** The same results were obtained by Sellden and Lindahl in 1999, after they have studied 45 patients receiving amino acids before anesthesia and 30 control patents receiving acetated Ringer's solution 21.Kasai et al; 2003 investigated whether such stimulation also occurs during spinal anesthesia, which blocks sympathetic nervous activity. They examined the effect of i.v. amino acid infusion on changes in core temperature during spinal anesthesia. They found that Amino acid infusion caused an increase in core temperature, and the core temperature values after 30 min of amino acid infusion were significantly higher than those in the control group [25].

In 2005, Chandrasekaran et al, conducted a pilot study on 10 patients underwent complex major colorectal operations who received amino acids infusion just after induction of anesthesia but prior to skin incision and 10 control patients who underwent similar surgical procedures. They found that the body temperature was statistically significantly reduced in both groups at skin incision when compared with temperature prior to induction of anesthesia. However, the

increase in body temperature after this initial reduction till recovery period was statistically significant in the study group but not so in the control group [26].Kamitani et al showed in 2006, that amino acids infusion started at induction of anesthesia in 42 patients (duration of surgery of 180 min or more) prevented intraoperative hypothermia, and their infusion in 32 patients (duration of surgery less than 180 min) decreased significantly the number of patients with tympanic temperature of less than 35.5^{o}C as compared with saline infusion [27]. 180 patients underwent off-pump coronary artery bypass grafting were included in a study conducted by Umenai et al in 2006. esophageal core temperatures became significantly higher in the amino acid infusion group than in the saline infusion group from 150 min after induction of anesthesia until the end of surgery [28].

Rectal-to-skin temperature gradient was identical in the four groups even when the core temperature was higher in the amino acids treated groups during the plateau phase of anesthesia-induced hypothermia and during early postoperative period which indicates that the threshold for thermoregulatory vasoconstriction was synchronously elevated in these groups[23].

This vasoconstriction was most probably responsible for the marked progressive increase in the rectal-to-skin temperature gradient that was observed after two hours from the onset of anesthesia then decreased gradually as the core temperature was approaching its resting value. The mechanisms by which amino acid infusion increases the set point are not clear and remain unknown. However, peripherally infused amino acids are unlikely to cross the blood-brain barrier. It is therefore unlikely that amino acids directly alter central thermoregulatory control[23].

As regard hemodynamics, amino acids infusion was proved to have no significant effects on heart rate or mean arterial pressure when compared with infusion of the same amount of saline in awake, non-anesthetized volunteers [23].On the other hand, hypothermia and anesthesia itself have profound effects on hemodynamics.

As observed in the present study, many other researchers showed that there was no significant difference in heart rate between the studied groups during preoperative, intra-operative or postoperative periods [29].

Furthermore, the reduced heart rates in the previous studies, despite of being statistically significant, it was clinically insignificant as it was less than 10 beats/min at any given time. So, it was concluded that the changes in the mean heart rate observed in the current study were only attributed to the effect of surgery and anesthesia.

As regard mean arterial blood pressure, it was proved that mild hypothermia produces hypertension due to the thermoregulatory vasoconstriction[30].During anesthesia, this vasoconstriction is developed only after two to three hours and strongly related to the level of serum norepinephrine [31].

In the current study, there were no significant differences between the four groups throughout

anesthesia and surgery, but there was a statistically significant difference between the control groups and amino acid treated groups mainly in the early postoperative period during which the control groups showed statistically significant higher MAP than the other groups. This is constant with the findings reported by Sellden et al in 1996 [24].

In a more recent study, Sellden and Lindahl obtained the same results in 1998 by measuring the arterial blood pressure, heart rate and plasma adrenaline and noradrinaline levels in 14 patients scheduled for gall bladder surgery. They found that there were no significant differences between patients receiving amino acids infusion and those receiving nutrient-free saline [29]. Although a study showed that there was no significant difference in blood pressure postoperatively between normothermic and mild hypothermic patients underwent cerebral aneurysm surgeries [32].

This controversy is most probably attributed to the big significant difference in the core temperature between the two studied groups compared with that of our study; as the hypothermia-induced bradycardia is temperature dependent; it is not surprising that a significant difference in heart rate between the studied groups could not be detected in the current study. Yet a more recent study showed that a significantly higher blood pressure was recorded in hypothermic patients on arriving to PACU [33].

In the current study the four groups showed comparable serum lactate level throughout the study period except for mild increase observed in the control group postoperatively. This increase, although statistically significant, was clinically insignificant because its maximum value was 1.8±0.33 mmol/l (mean±SD) i.e. less than 2 mmol/l. moreover, this increase decreased significantly after 2 hours.

The increased serum lactate level in the control group postoperatively can be explained therefore, to be the result of increased muscular activity in the majority of patients in this group in the form of shivering which was suppressed later on if it was vigorous or annoying.

All of these evidences suggested that either mild hypothermia, nor amino acids infusion have no direct effect on serum lactate level and only a mild-within normal-elevation of its level might be observed during mild hypothermia most probably caused by shivering and not by hypothermia itself [34].

Consequently, as the metabolic and the respiratory factors of acid-base balance were kept within normal range, the bicarbonate levels were expected to be comparable between the studied groups, which was supported by the actual observation of its levels.

As regard laboratory findings, the four studied groups showed comparable trends for serum glucose without between–groups significant difference. Serum glucose level increased significantly during the intraoperative period till reached the peak (about 113 mg/dl) immediately postoperative then the level started to decrease later postoperatively but it was significantly higher in control groups than the amino acid infused groups.

Similarly, serum cortisol levels were comparable between the four groups. There were no statistical significant differences between the four groups pre-operatively and intra-operatively and post-operatively, but There was progressive increase in these levels to reach the maximum value immediately postoperatively, two hours postoperatively, serum cortisol levels started to decrease, but didn't reach the baseline value

Hypothermia was proved to produce hyperglycemia [35] and decrease in levels of the stress response hormones including cortisol [32]**.** However, serum glucose and serum cortisol levels are not affected by the hypothermia only. Being parts of stress response to surgery, their levels may vary markedly intra- and postoperatively [36]**.**

Therefore, it is not surprising that; in the study conducted by Frank et al in 1995, serum levels of both substances increased significantly in both the mild hypothermia group (37 patients) and the normo-thermia group (37 patients) during the early postoperative period, without between-groups significant differences [37].

Consequently, the observed trend of both serum levels in the present study (as well as in Frank et al study) could be attributed to the surgical stress with very minimal contribution of hypothermia as it was reported to be mild even in the control group. These comparable between-groups levels suggested that the augmented thermogenic effect of amino acids during and at emergence from anesthesia occurs without imposing any additional stress in surgical patients [29]

As regard postoperative pain, there was significantly lower VAS in group Ia and group IIa than the control group particularly in the early postoperative period. This may be attributed-again-to the higher incidence of shivering in the control group which sometimes increases the pain perception by stretching surgical incisions in addition to the annoying cold sensation [5].

Shivering was controlled in all the studied patients within the first hour after recovery. This lower incidence of shivering due to preoperative infusion of amino acids was constant with the findings obtained in 2002 by Sahin and Aypar who studied forty craniotomy patients assigned into four different groups according to the anesthetic technique and whether or not they received amino acid infusion. They found that shivering intensity was less in the two amino acid treated groups [38].

Administration of amino acids in group Ia and group IIa was effective in prevention of postoperative shivering as indicated by the incidence of shivering-free patients in these groups. On the other hand, the control group showed marked; significantly higher incidence of shivering needed the rescue mepridine injections.

Conclusion:

In conclusion, this study showed that amino acid infusion before anesthesia (general or regional) and surgery restored core body temperature at awakening and almost eliminated postoperative shivering and the related adverse effects without uncompensated extra-hemodynamic or metabolic loads.

Recommendations:

It is recommended to start the amino acid infusion one hour before the induction of anesthesia for operations lasting between two to four hours and in general, the onset of amino acids infusion has to be tailored according to the expected duration of surgery keeping in mind delayed thermogenic effect of amino acid infusion.

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