Effect of perioperative amino acid infusion on intraoperative hypothermia and postoperative shivering during pelvi-abdominal surgery in cancer patients

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ABSTRACT

Background: This study evaluated the effect of perioperative infusion of amino-acid and Ringer solutions on intraoperative hypothermia (by measuring esophageal and skin temperature), amount of blood loss and transfusion requirement, duration of recovery and hospital stay and postoperative shivering.

Methods: Forty Two cancer patients scheduled for pelvi-abdominal surgery were randomly allocated into two equal comparable groups. The first group (Aminoven group) received Aminoven 10% solution while the second group (Ringer group) received warm Ringer solution. Evaluated variables included esophageal and skin temperature, amount of blood loss and transfusion requirement, duration of recovery and hospital stay and postoperative shivering.

Results: Aminoven group and Ringer group there is significantly difference in core and skin temperature, amount of blood loss and transfusion requirement, duration of recovery and hospital stay and postoperative shivering.

Conclusions: Our findings suggest that Amino acid infusion before anesthesia and surgery restored core body temperature and almost

eliminated postoperative shivering and the related complications of hypothermia

Key words: Amino acid-core temperature-shivering-hypothermia-complication

Introduction

Hypothermia, defined as a core body temperature less than 36 ^{0}C, is a relatively common occurrence in the surgical patient. A mild degree of perioperative hypothermia can be associated with significant morbidity and mortality.[1]

Human thermoregulating system allows ranges from 0.2 to 0.4 ^{0} C around 37 ^{0}C to maintain metabolic functions.[2] subsequently hypothermia results largely from heat loss exceeding metabolic heat production.[3]

During anesthesia and surgery, core temperature rapidly drops by (0.8-1 ^{0}C) in the first hour of surgery, this decrease is then more gradual until it stabilizes the latter happens when heat production is equal to heat loss. Preventive measures are directed to minimize the heat loss by decreasing temperature gradient between the patient and surrounding environment.[4]

Intraoperative hypothermia is a major adverse effect of general anesthesia. This results mainly from a decrease in energy expenditure and heat generation during general anesthesia[5], together with a reduced threshold to initiate heat conservation.[6] Several complications are associated with intraoperative hypothermia, such as wound infection[7] and impaired

coagulation.[8] Thus, improved thermal care in the perioperative period has attracted interest.

Infusion of certain nutrients is an alternative approach to increase metabolic heat production, thus reducing the disparity between heat production and loss. The primary basis for this approach is the increase in energy expenditure that follows infusion of certain nutrients, a response known as diet-induced thermogenesis.[9, 10]

Facultative thermogenesis is best characterized for amino acids which increase metabolic rate, thereby augmenting perioperative core temperature.[11, 12]

It is well established that amino acid infusions induce perioperative thermogenesis and help prevent hypothermia.[13]

The mechanisms that underlie these findings were possibly related to the augmented level of energy expenditure. An increased threshold core body temperature for thermoregulatory vasoconstriction during surgery might also contribute partly to the maintenance of body core temperature.[14]

Interestingly, amino acid infusions also increase all major autonomic thermoregulatory defense thresholds and resting core temperature. These mechanisms predominantly occur in extra-splanchnic tissues. Amino acids thus have both metabolic and thermoregulatory properties that help maintain intraoperative normothermia.[15]

Amino acid infusions started after development of intraoperative core hypothermia do not affect rewarming but reduce the incidence of postoperative shivering during major abdominal surgery.[16]

Patients and Methods

This study was carried at National Cancer institute, Cairo University, Egypt. It is a prospective study, phase III clinical trial. The study was carried on 42 cancer patients undergoing pelvi-abdominal surgery at NCI hospital from January 2016 to March 2017.

Eligibility criteria:

Inclusion criteria

1. ASA physical status I and II.
2. Age from 40 to 70 years old.
3. Duration of surgery of 180 minutes or more

Exclusion criteria

1. Patients admitted for gastro intestinal surgeries.
2. Those receiving vasodilators or medications likely to alter thermoregulation.
3. Febrile patients (body temperature more than 37.5^0C).
4. Hepatic or renal impairment.
5. History of cardiovascular or respiratory impairment.

All Patients were subjected to:

- Medical and anesthetic assessment by history and clinical examination.
- Basic investigations :
    - ✓ Complete blood count.
    - ✓ Liver and kidney functions.
    - ✓ Serum electrolyte level.

- ✓ Coagulation profile.

- Radiological investigations including Chest X-Ray.

After Approval of Institutional review board (IRB), Patients were randomly allocated using permuted block method into two equal treatment groups:

- ***Group One*** *(Aminoven group):* received Aminoven 10% solution (Fresinius-Kabi) through a central venous catheter at an infusion rate of 1 ml/kg/h (0.1 gm/kg/h) starting 2 hour before induction of anesthesia till the end of surgery using electric infusion pump (ATOM p-600).
- ***Group Two*** *(Ringer group):* received warm Ringer solution at a rate 10-15 ml/kg/h starting 2 hour before the induction of anesthesia using electric infusion pump (ATOM p-600).

After admission to the operation room and before induction of anesthesia, patients were covered with a cotton sheet preoperatively, and by drapes during surgery. Basic monitoring was attached to the patients in the form of pulse oximeter, blood pressure cuff and ECG. Anesthesia was induced by intravenous administration of fentanyl in the dose of 1-2 mcg/kg, 2 mg/kg Propofol and 0.5 mg/kg Atracurium bromide, and was maintained with 1.2% Isoflurane. Mechanical ventilation was adjusted to maintain end-tidal Pco_2 between 35 and 40 mmHg. A 20-g catheter was inserted into the left radial artery for blood pressure monitoring and blood sampling. A core temperature probe inserted esophygeally and skin temperature probe was attached to the patient forehead for temperature monitoring (G E temperature care cable dual 400-700 series). At the end of surgery smooth recovery was achieved and patient was transferred to PACU (Post anesthesia care unit).

Figure 1: G E temperature care cable dual 400-700 series with its probes

During surgery the following had been measured:

1. The temperature (After induction of anesthesia and every 30 minutes till the end of surgery)
   a) Core temperature (esophageal)
   b) Skin temperature
   c) Core- skin temperature gradient.
2. Amount of blood loss & transfusion requirement.

The following had been measured postoperatively:

1. Duration of postoperative mechanical ventilation (recovery from anesthesia).
2. The degree of postoperative shivering (using 4 point scale)[17]

   Grade 0: No shivering

   Grade 1: Mild fasciculation of face or neck

   Grade 2: Visible tremor involving more than one muscle group

   Grade 3: Gross muscular activity involving the entire body
3. Duration of hospital stay.

Results

Regarding the core temperature, it was significantly higher in the Aminoven group than the Ringer group during all times of the intraoperative period. (Table 1, Figure 2)

Table 1: Intraoperative core temperature from 30 min. to 4 hours in the two studied groups

	Aminoven group **n=21**	**Ringer's group** **n=21**	**p value**
Core Temperature (°)			
30 min.	36.8±0.2	35.5±0.2	< 0.001
60 min.	36.6±0.2	34.9±0.3	< 0.001
90 min.	36.4±0.2	34.4±0.3	< 0.001
120 min.	36.1±0.2	33.8±0.3	< 0.001
150 min.	35.9±0.2	33.3±0.2	< 0.001
180 min.	35.8±0.2	32.8±0.2	< 0.001
210 min.	35.6±0.2	32.4±0.2	< 0.001
240 min.	35.3±0.2	32.0±0.2	< 0.001

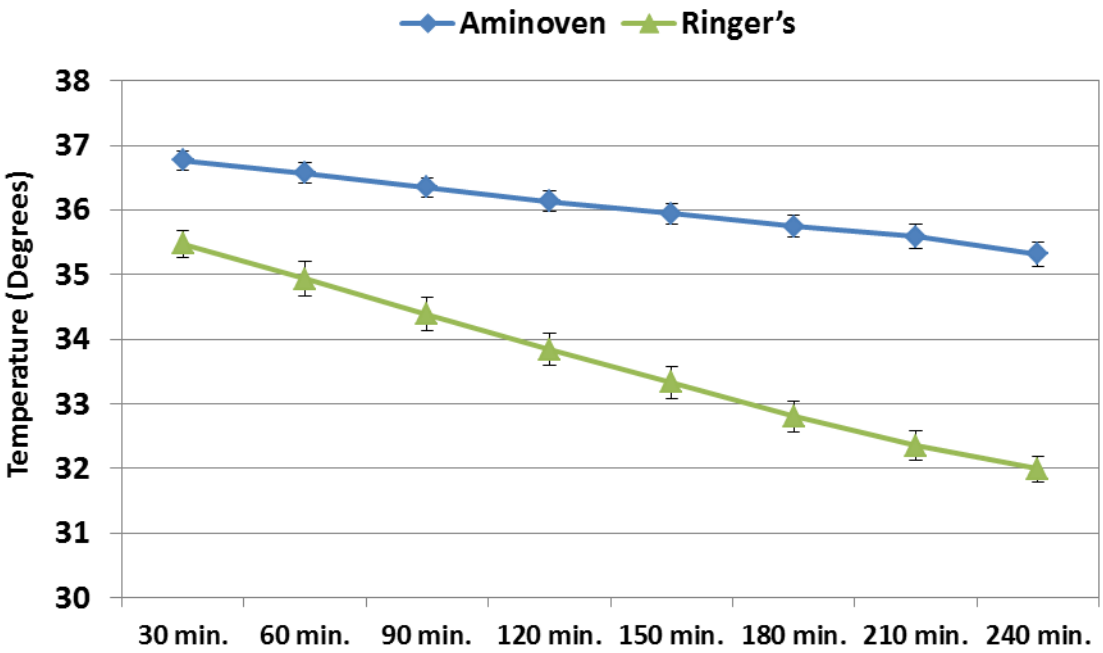

Figure 2: Core temperature during the intraoperative period up to 4 hours in the two studied groups.

During all times of the intraoperative period, the skin temperature of Aminoven group was significantly higher than Ringer's group. (Table 2, Figure 3)

Table 2: Intraoperative skin temperature from 30 minutes to 4 hours in the two studied groups

	Aminoven group n=21	**Ringer's group n=21**	**p value**
Skin Temperature (°)			
30 min.	35.2±0.2	33.9±0.2	< 0.001
60 min.	35.0±0.2	33.4±0.2	< 0.001
90 min.	34.8±0.2	32.7±0.3	< 0.001
120 min.	34.6±0.2	32.1±0.3	< 0.001
150 min.	34.4±0.2	31.6±0.3	< 0.001
180 min.	34.2±0.2	31.0±0.3	< 0.001
210 min.	34.0±0.2	30.6±0.4	< 0.001
240 min.	33.7±0.2	30.2±0.3	< 0.001

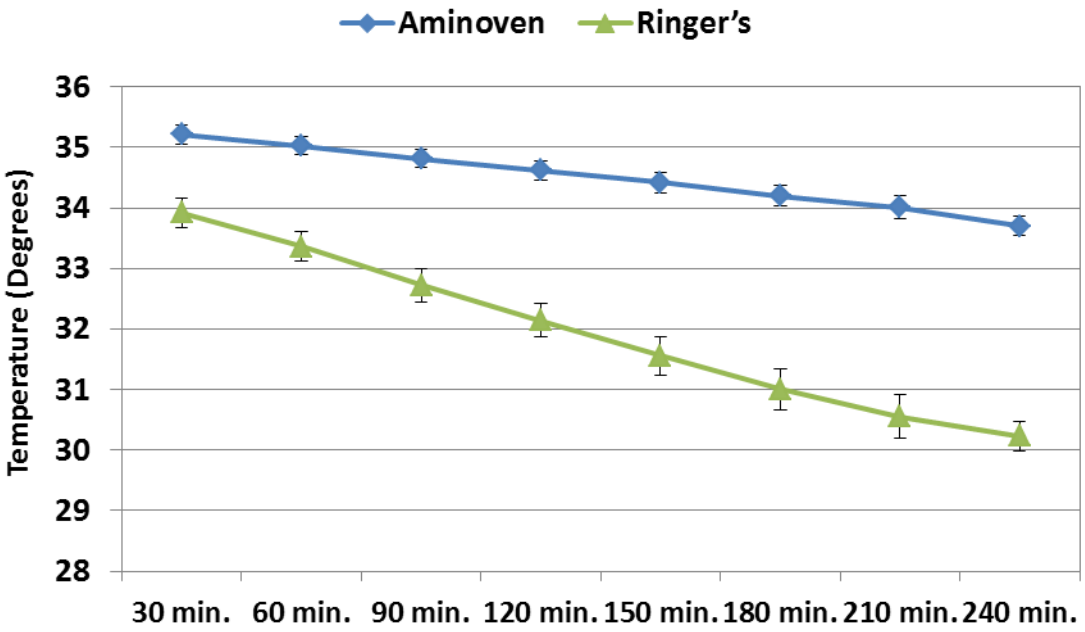

Figure 3: Skin temperature during the intraoperative period up to 4 hours in the two studied groups.

Intraoperative blood loss was significantly higher in Ringer's group compared to Aminoven group. Blood transfusion was significantly lower in Aminoven group compared to Ringer's group. (Table 3)

Hospital stay and duration of recovery (duration of postoperative mechanical intubation) were significantly longer in Ringer's group compared to Aminoven group. (Table 3)

Table 3: Blood loss and transfusion volumes, duration of recovery and hospital stay in the two studied groups

	Aminoven group n=21	**Ringer's group n=21**	**p value**
Blood loss	824±257	1100±305	0.003
Blood transfusion	643±244	969±287	< 0.001
Duration of recovery	14.5±4.2	21.0±4.6	<0.001
Hospital stay	4.1±1.3	5.7±1.8	0.002

Regarding Shivering; Grades 0 and 1 shivering were significantly higher in Aminoven group compared to Ringer's group. Grade 2 shivering was comparable in the two groups. Grade 3 shivering was seen only in the Ringer's group ($p < 0.001$). (Table 4)

Table 4: Degree of postoperative shivering in the three studied groups

	Aminoven group n=21	**Ringer's group n=21**	**p value**
Degree of shivering			
Grade 0	4 (19.0%)	0 (0.0%)	0.001
Grade 1	10 (47.6%)	5 (23.8%)	
Grade 2	7 (33.3%)	6 (28.6%)	
Grade 3	0 (0.0%)	10 (47.6%)	

Discussion

Unintentional perioperative hypothermia, defined as core blood temperature below 36ºC, is a common event, due to direct thermoregulation inhibition of anesthetics, decreased metabolism and exposure to the cold environment of operating room.[18]

The best management for hypothermia, like most complications in anesthesia, is prevention. Prevention starts with preoperative preparation of the patient and the operating environment.[19]

Many warming devices are in use to prevent heat loss, but little attention has been paid to stimulate the body's own heat generation.[20]

Infusion of certain nutrients is an alternative approach to increase metabolic heat production, thus reducing the disparity between heat production and loss. The primary basis for this approach is the increase in energy expenditure that follows infusion of certain nutrients, a response known as diet-induced thermogenesis.[9, 10]

The objective of this study was to compare the effect of perioperative infusion of amino-acid and Ringer's acetate solutions on intraoperative hypothermia by measuring esophageal and skin temperature, amount of blood loss and transfusion requirement, duration of recovery and hospital stay and postoperative shivering.

Regarding the core and skin temperature, this study revealed that during all times of the intraoperative period, the core and skin temperature of the Aminoven group was significantly higher than the Ringer’s group.

Throughout surgery, the reduction in core and skin temperature was more marked in the Ringer's group than Aminoven group. (P value< 0.001), thus preoperative amino acids infusion induces thermogenesis and minimize intraoperative hypothermia because Facultative thermogenesis is best characterized for amino acids which increase metabolic rate, thereby augmenting perioperative core temperature[11, 12] the mechanisms that underlie these findings were possibly related to the augmented level of energy expenditure. An increased threshold core body temperature for thermoregulatory vasoconstriction during surgery might also contribute partly to the maintenance of body core temperature[14] these mechanisms predominantly occur in extra-splanchnic tissues. Amino acids thus have both metabolic and thermoregulatory properties that help maintain intraoperative normothermia.[15]

In agreement with our results, **Yasuki Fujita et al (2014)** randomly assigned the patients to the amino acid (A), amino acid and glucose (AG), or control (C) groups and the body temperature changes were compared to baseline values before surgery. Body temperatures in Group A rose continuously and increased gradually above the baseline, and were significantly increased compared with baseline and with Groups AG and C in each period ($p < 0.05$). The patients in Group C displayed significantly decreased body temperatures throughout surgery.[21]

Also, **Zhou et al (2014)** reported that crystalloid solution infusions caused a greater drop of core body temperature in patients, compared to amino acid infusions ($p<0.00001$).[22]

Moreover, **Zhong J et al (2012)** showed that nasopharyngeal temperature values, which decreased during surgery in both groups, were significantly higher in group AA than in group LR from T3 to T5.[23]

Another study done by **Moriyama et al (2008)**, they mentioned that 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 ($P<0.005$).[24]

Also, **Umenai T. et al (2006)** prospectively determined the effect of amino acid infusion on esophageal core temperature and postoperative outcomes during off-pump coronary artery bypass grafting (CABG). One-hundred and eighty consecutive patients undergoing primary elective or urgent off-pump CABG were randomly divided into two groups: the IV amino acid infusion group and the saline infusion group. The esophageal core temperature at the end of surgery was 35.6 (35.3–35.8) °C in the saline infusion group and 36.1°C (35.9–36.3) °C in the amino acid infusion group ($P = 0.01$).[25]

Also, **Nagy Ali et al (2006)** reported that mean final core temperature 120 min. after induction of spinal anesthesia was 34.37 (SD 0.37) ^{0}C in the saline group and 36.02 (SD 0.21) ^{0}C in the amino acid group ($p < 0.05$).[26]

Also**, Widman Jan et al (2002)** showed that the baseline temperature before amino acid or acetated Ringer's infusion and spinal anesthesia was 36.6°C ± 0.3°C and 36.9°C ± 0.3°C in the amino acid and control groups, respectively. During 1 h of amino acid infusion before the induction of spinal anesthesia, the mean core temperature increased by 0.3°C ± 0.2°C from baseline values ($P < 0.001$), whereas it was unchanged in the controls

receiving Ringer's acetate. Throughout surgery, the reduction in core temperature was more marked in the control group than in the amino acid group. At the end of surgery, the average decrease in core temperature from baseline was significantly larger in the controls (0.9°C ± 0.4°C) than in the amino acid patients (0.4°C ± 0.3°C) ($P < 0.01$).[27]

In contrast with our findings, **Sheryl Warttig et al (2016)** observed significant statistical heterogeneity in the results. Some trials showed that higher temperatures were associated with amino acids, but not all trials reported statistically significant results, and some trials reported the opposite result, where the amino acid group had a lower core temperature than the control group. Amino acids led to a statistically significant increase in core temperature in comparison to those receiving control.[28]

In our study, regarding the intraoperative blood loss, it was significantly higher in Ringer's group (1100±305 ml) compared to Aminoven group (824±257) This may be attributed to hypothermia causes decreased coagulation factor activity leading to a greater intraoperative bleeding and blood loss.[29]

Blood transfusion was significantly lower in Aminoven group (643±244 ml) compared to Ringer's group (969±287 ml). This might reflect the fact that the thermogenic effect of amino acid infusion was mainly exerted during anesthesia and surgery.[27]

In agreement with our results, **Widman Jan et al (2002)** showed that intraoperative blood loss was significantly larger in control patients at the end of surgery (702 mL; range, 90–1220 mL) than in patients who received amino acids (516 mL; range, 130–1490 mL) ($P < 0.05$). There were no

significant differences in shed blood volume or in the administered volume of allogenic blood between the two study groups during the 24-h study period. Initial hemoglobin concentrations did not differ between the two study groups and the decrease after surgery and on the first postoperative day was similar.[27]

Also, **Nagy Ali et al (2006)** showed that intraoperative blood loss was significantly larger in the saline group than in the amino acids infusion group ($p < 0.05$).[26]

Regarding postoperative shivering, in our study; Grades 0 and 1 shivering were significantly higher in Aminoven group (14 patients) compared to the Ringer's group (5 patients). Grade 3 shivering was seen only in the Ringer's group (10 patients).This may be attributed to amino acids infusion has both metabolic and thermoregulatory properties that maintain intraoperative normothermia and prevent postoperative shivering.[15]

Hospital stay and duration of recovery (duration of postoperative mechanical intubation), in our study, were significantly longer in Ringer's group compared to Aminoven group. This may be attributed to the thermogenic effect of amino acids infusion that reduce the duration of mechanical ventilation and enhance recovery from anesthesia.[15]

In agreement with our results, **Zhou B. et al (2016)** showed that the occurrence of shivering ($p=0.0001$) in the groups having amino acid infusions were lower than the group of studies having crystalloid solution infusions. Additionally, compared with crystalloid solution infusions, amino acid infusions shorten duration of postoperative mechanical intubation ($p<0.0001$) and duration of hospitalization ($p<0.00001$).[30]

Also, **Mohamed Aly et al (2010)** showed that postoperative shivering was significantly more frequent and more intense in the control group than in the other two groups during the first hour postoperatively.[31]

Another study done by **Umenai T. et al (2006)**, they showed that patients who received amino acids, there was a shorter duration of mechanical ventilation after surgery (P=0.01), time in the ICU stay (P=0.001), and days until fit for discharge from hospital after surgery (P=0.004) than those given saline.[25]

Also **Nagy Ali et al (2006)** showed that the incidence and degree of shivering were significantly higher in control group than in amino acids infusion group (p value < 0.05).[26]

It is important to emphasize the advantages of perioperative amino acids infusion. It is more thermogenic than warm Ringer solution (Facultative thermogenesis is best characterized for amino acids), less degree of shivering, less amount of blood loss and transfusion requirement, less duration of recovery and hospital stay.

Conclusion

Unintentional perioperative hypothermiais a common event during general anesthesia. The best management for hypothermia is prevention. We need more attention to be paid to stimulate the body's own heat generation. Amino acid infusion before anesthesia and surgery restored core body temperature and almost eliminated postoperative shivering and the related adverse effects of hypothermia without uncompensated extra-hemodynamic or metabolic loads.

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الملخص العربى

أثر التنقيط الوريدى للاحماض الامينية على انخفاض حرارة الجسم والارتعاش ما بعد الجراحة أثناء جراحات البطن والحوض لمرضى الأورام

يحدث الانخفاض في حرارة الجسم حينما تصل درجة حرارة الجسم الأساسية لأقل من ٣٦ درجة مئوية ، وهو حدوث شائع نسبيًا في المرضي الذين يخضعون للعمليات الجراحية ومن الممكن أن انخفاض بسيط في معدل درجة الحرارة أن يكون مصحوبًا بمعدل عالي من المراضة والوفيات.

يتم توجيه التدابير الوقائية للحد من فقدان الحرارة إلى الحد الأدنى عن طريق خفض التدرج في درجة الحرارة بين المريض والبيئة المحيطة. وقد افترضت الأحماض الأمينية لتحفيز إنتاج الحرارة وتقليل فقدانها عن طريق خفض تدفق الدم إلى الأطراف نتيجة الانقباض في الأوعية الدموية.

وكان هدف هذه الرسالة هو مقارنة أثر التنقيط الوريدي من الأحماض الأمينية ومحلول الرنجر قبل وأثناء العمليات الجراحية على انخفاض حرارة الجسم الأساسية (تقاس هنا عن طريق المرئ) ودرجة حرارة الجلد، كمية الدم المفقودة اثناء الجراحة، مدة الافاقة من التخدير، درجةالارتعاش بعد العملية الجراحية ومدة الاقامة فى المستشفى. شملت هذه الدراسة على ٤٢ مريضا وتم تقسيمهم الى مجموعتين متساويتين: المجموعة الاولى (مجموعة الامينوفين)، اما المجموعة الثانية (مجموعة الرينجر).

في دراستنا ، خلال جميع الأوقات من فترة العملية ، كانت درجة الحرارة الأساسية ودرجة حرارة الجلد في مجموعة الأمينوفن أعلى بكثير من مجموعة الرنجر.وكذلك درجة الارتعاش وكمية الدم المفقودة كانت اقل فى مجموعة الامينوفين.

ضخ الحمض الأميني في الدم قبل التخدير والجراحة يعمل على استعادة درجة حرارة الجسم الأساسية والقضاء تقريبًا على الارتعاش الشديد بعد العملية الجراحية والآثار السلبية ذات الصلة من انخفاض حرارة الجسم دون تأثير على الدورة الدموية.