

Effect of amino acid infusion on perioperative thermoregulation in newborn surgery

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ABSTRACT

Objectives: Decreased drug metabolism, coagulation disorders, wound infections, and cardiac arrhythmias are the most important and well-known results of intraoperative hypothermia. Perioperative amino acid infusion is known to prevent intraoperative hypothermia during general anesthesia in adults. In this study, we aimed to demonstrate the effect of perioperative amino acid infusion on the prevention of hypothermia during general anesthesia in newborn surgery.

Methods: Twenty surgical newborns, aged 1-30 days, were enrolled in this prospective randomized controlled study. Newborns were assigned randomly into two groups: the amino acid/dextrose (AAD) group and the dextrose (D) group. The core temperatures of the newborns were measured from the distal esophagus in the first minute of the induction once and every fifteen minutes thereafter. The core body temperature changes in each group during the operation and the differences between the two groups were analyzed.

Results: The surgical operations in each group were similar. The mean operating room temperatures of AAD and D groups were $25.4 \pm 0.2^\circ\text{C}$ and $25.3 \pm 0.3^\circ\text{C}$, respectively. There were no significant differences in the general characteristics of the two groups. The mean core temperatures began to decrease after the induction of anesthesia in both groups and continued to decrease during the course of the surgery. There was no significant difference between the two groups.

Conclusions: Hypothermia develops in all neonates when surgical time exceeds one hour, even in warmer ambient temperatures. Although it seems effective in adults, amino acid-induced thermoregulation does not seem effective in newborns during general anesthesia.

Keywords: Amino-acid, anesthesia, hypothermia, newborn, thermoregulation

Decreased metabolic rate and impaired thermoregulation during general anesthesia cause significant undesirable effects, even in adults [1, 2]. Newborns, having a larger surface area and less subcutaneous fatty tissue covering central structures, are more susceptible to these inadvertent effects. Decreased drug metabolism, coagulation disorders, wound infections, and cardiac arrhythmias are the

most important and well-known results [3, 4].

Core body temperature has to be kept at a constant level (37°C) in each environment for the continuation of metabolic functions [2]. Peripheral arteriovenous shunts, sweating, shivering, and non-shivering heat generation constitute important intervention mechanisms in conscious individuals [3]. General anesthesia and surgery are frequently accompanied by hypother-

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mia related to the impairment of thermoregulation and synchronous reduction of vasoconstriction thresholds and shivering [1]. Body heat is redistributed from the core to the periphery shortly after induction of anesthesia and results in a decrease in core temperature. The course is followed by heat loss exceeding metabolic heat production.

Patients can be intensively warmed or simply kept warm either by elevating the ambient temperature or by the use of extracorporeal devices such as forced-air warming blowers and infusion fluid warming devices during general anesthesia [3, 5]. As a different approach, perioperative amino acid infusion is known to prevent intraoperative hypothermia during general anesthesia in adults [6-11].

Due to the high amount of brown adipose tissue, non-shivering thermogenesis is used in preference to shivering in newborns [1, 12-14]. Despite all compensatory mechanisms, newborns have a limited capacity for thermoregulation and are prone to hypothermia. Although there are several studies about amino acid-induced thermoregulation in adults, there is no study in newborns and infants related to the subject. In this study, we aimed to demonstrate the effect of perioperative amino acid infusion on the prevention of hypothermia during general anesthesia in surgical newborns.

METHODS

The study protocols were reviewed and approved by the ethics committee of İstanbul University, İstanbul School of Medicine. All parents were informed about the study before giving their consent to participate. Twenty surgical newborns, aged 1-30 days, were enrolled in this prospective, randomized controlled study. Newborns with fever, sepsis, and those undergoing surgical procedures shorter than 60 min were not included in the study.

Newborns were randomly divided into two groups: the amino acid and dextrose 10% infusion group (AAD) and the 10% dextrose only infusion group (D). Amino acid (TrophAmine® 6%, B. Braun Hessen, Germany) solution was given at a rate of 1g/kg-1 24 h-1 and dextrose 10% solution was given at a rate 100 mL kg-1 24h-1 before and during the operation.

No premedication was given before surgery. The ambient operating room temperature was maintained near 25°C. All newborns received general anesthesia with sevoflurane and air O₂. Tracheal intubation was facilitated with rocuronium. Ventilation was controlled and adjusted to keep end-tidal CO₂ at 4.6-5.2 kPa (35-40 mm Hg). All newborns were placed on warm gel pads, which were placed on a constant electrical heating pad that was adjusted to 37°C (KanMedOperatherm 202; KanMed AB, Bromma, Sweden). A heat and moisture exchanger was connected to the tracheal tube connector in all newborns. The head, legs, and arms were covered by warm cotton.

The age, sex, weight, hemoglobin concentration, primary pathology, preoperative infusion time, duration of anesthesia, the initial core temperature of the newborns, and the ambient operating room temperature were recorded. The core temperatures of the newborns were measured from the distal esophagus in the first minute of the induction once and every fifteen minutes thereafter. Thermocouple probes (Ellab YRY-T, Ellab, Hillerod, Denmark) were connected to the Mennen Horizon XL monitor (Mennen Medical Ltd., Rehovot, Israel).

Statistical Analysis

The core body temperature changes in each group during surgery and the differences between the two groups were analyzed. Statistical analysis was performed using the SPSS 11 package program. Descriptive data are expressed as mean ± standard deviation and number (%). Continuous variables are given as mean ± standard deviation and categorical variables as percentage (%). Independent group comparisons were made using Student's t-test when parametric test assumptions were provided. The Mann-Whitney U test was used when parametric test assumptions were not provided. The Chi-square test was used to determine categorical variables. *P* values < 0.05 were considered statistically significant.

RESULTS

A total of 20 surgical newborns were enrolled in the study. The diagnoses of the newborns are shown in Table 1. The surgical operations in each group were

Table 1. Diagnosis of the patients

Dextrose (D) group	Amino acid and dextrose (AAD) group
Midgut volvulus	Gastric perforation
Congenital diaphragmatic hernia	Pyloric atresia
Congenital diaphragmatic hernia	Duodenal atresia
Duodenal atresia	Midgut volvulus
Malrotation	Volvulus and internal hernia
Pyloric stenosis	Gastric perforation
Pyloric stenosis	Ileal atresia
Necrotizing enterocolitis	Congenital diaphragmatic hernia
Malrotation	Meconium ileus
Intraabdominal cystic mass	Pyloric stenosis

similar. Operating room temperatures were constant within the limit of $\pm 0.5^{\circ}\text{C}$ for each group during the course of surgery. The mean operating room temperatures of the AAD and D groups were $25.4 \pm 0.2^{\circ}\text{C}$ and $25.3 \pm 0.3^{\circ}\text{C}$, respectively.

Table 2 illustrates the perioperative data for the two groups. There were no significant differences in the general characteristics of the two groups. The pre-operative infusion times in the AAD and D groups were 14.7 ± 4.9 hours and 15.1 ± 6.3 hours, respectively.

The mean core temperatures began to decrease after the induction of anesthesia in both groups and continued to decrease during the course of surgery (Fig. 1). Although the mean core temperatures in the AAD group were higher than in the D group during the entire surgical period, there was no significant difference between the two groups except at the 45th and 90th minutes of the operation (Table 3).

Table 2. General characteristics of two groups

	AAD	D	p value
Female	6	4	-
Age (day)	9.8 ± 9.1	10.7 ± 12.3	0.185
Weight (gram)	3037 ± 204	2800 ± 702	0.319
Hemoglobin (gr/dl)	14.00 ± 0.89	14.27 ± 2.7	0.710
Body Temperature ($^{\circ}\text{C}$)	36.5 ± 0.1	36.4 ± 0.2	0.200
Ambient Temperature ($^{\circ}\text{C}$)	25.4 ± 0.2	25.3 ± 0.3	0.545
Infusion Time (preop) (h)	14.7 ± 4.9	15.1 ± 6.3	0.877

AAD = amino acid/dextrose group, D = dextrose group

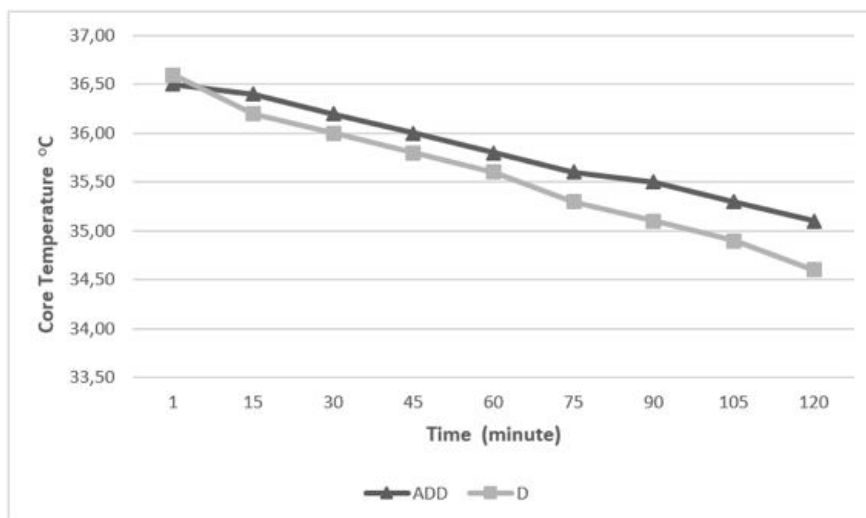


Fig. 1. Core body temperature changes in both groups.

Table 3. Measured core temperatures and differences

Time (min.)	AAD	D	p value
1.	36.50 ± 0.14	36.60 ± 0.13	0.103
15	36.4 ± 0.19	36.2 ± 0.19	0.083
30	36.2 ± 0.21	36 ± 0.18	0.132
45	36.0 ± 0.2	35.8 ± 0.2	0.018*
60	35.8 ± 0.3	35.6 ± 0.2	0.138
75	35.6 ± 0.4	35.3 ± 0.3	0.180
90	35.5 ± 0.4	35.1 ± 0.2	0.043*
105	35.3 ± 0.5	34.9 ± 0.3	0.128
120	35.1 ± 0.7	34.6 ± 0.2	0.185

AAD = amino acid/dextrose group, D = dextrose group, * $P < 0.05$

DISCUSSION

General anesthesia impairs thermoregulation and causes mild hypothermia in surgical patients. Anesthesiologists and surgeons use various approaches and combinations to keep patients normothermic. Unfortunately, it has not yet been possible to solve the problem completely. However, there is one additional internal warming method that has been known since the 1990s: amino acid-induced thermoregulation. Amino acids infused in the body stimulate both protein synthesis and breakdown and also increase blood flow, especially in extrasplanchnic tissue [15].

All reactions require larger amounts of energy compared with glucose or lipid metabolism, leading to accumulating heat in the body [11]. After Sellden *et al.* reported that amino acid infusion prevented perioperative hypothermia during anesthesia without any additional sympathoadrenal activity and shortened hospital stay [6, 15, 16], Kasai *et al.* [8] reported perioperative amino acids maintained core temperature and were useful in preventing hypothermia not only during general anesthesia but also during spinal anesthesia. A contribution to the subject also came from Nakajima *et al.* [10]; amino acid infusion increased both metabolic rates and resting core temperature, but they also produced a synchronous increase in all major autonomic thermoregulatory defense thresholds at the same time.

Non-shivering thermogenesis (activation of brown fat by an uncoupling protein, thermogenin) is used in preference to shivering in infants and in small mam-

mals [1, 12, 14]. It is thought that because of their high amounts of brown adipose tissue and their high potential for non-shivering thermogenesis, newborns should be able to produce more heat to compensate for heat loss in general anesthesia, but this is not the case. Newborns, like adults, are unable to respond to intraoperative hypothermia because inhibition of non-shivering thermogenesis occurs during general anesthesia [17-19]. In these circumstances, it might be considered that perioperative infusion of amino acids would increase heat formation via potentiation of non-shivering thermogenesis. However, the results of the current study do not support this hypothesis. Although the mean temperature of the AAD group was higher during anesthesia, the difference was not statistically significant.

Limitations

First, the operating room temperature could only be adjusted to about 22-23°C instead of 25°C, so a further decrease in body core temperature might have led to an increase in the thermogenic effect of amino acids. On the other hand, this could be more realistic because most of the time the operating room temperature was around 21-22°C. Although the optimal delivery room temperature is recommended to be 25-28°C, it is also a fact that 25°C is an uncomfortable temperature for all operating room staff [20].

Second, we could have given an amino acid solution without dextrose during the surgery because glucose supplementation inhibits endogenous glucose production and stimulates insulin secretion to a greater

extent than the administration of amino acids alone in adults. Moreover, intraoperative exogenous glucose suppresses protein catabolism and gluconeogenesis. Therefore, excessive glucose administration may disturb amino acid-mediated thermogenesis [21]. According to Fujita *et al.* [22], intraoperative amino acid infusion without glucose administration appears to be more effective for body temperature maintenance in patients undergoing colorectal surgery. However, we thought that it would be inappropriate to give amino acid solutions alone in newborns who are prone to hypoglycemia in long surgical procedures.

Third, there may be a linear relationship between the amount of amino acids and the thermogenic effect. Some groups given different amount of amino acids could be added.

In addition, cold ambient room temperature (below 23°C) can significantly interfere with the maintenance of core temperature in newborns and infants during anesthesia. However, neonates cannot maintain their core temperature, even in warmer operating room temperatures [5]. Despite taking all necessary precautions, as mentioned previously, we observed mild hypothermia in both groups during surgery. Hypothermia developed in all newborns when surgical time exceeded one hour, even though the operating room temperature was around 25°C.

CONCLUSION

Hypothermia develops in all neonates when surgical time exceeds one hour, even in warmer ambient temperature. Although it seems effective in adults, amino acid-induced thermoregulation does not seem effective in newborns during general anesthesia. This effect may be dose-dependent. Studies with more groups and different amino acid doses are needed.

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All procedures performed in studies involving human participants were accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Both authors were working in Istanbul University during the study.

Authors' Contributions

Conception and design: M.O, F.T.S; Data analysis interpretation: M.O, F.T.S; Manuscript writing and revision: M.O, F.T.S

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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