http:// ijp.mums.ac.ir
Original Article

Evaluation of the Effect of Amino Acid Administration on Hypothermia during General Anesthesia in Hypospadias Surgery on Children Aged 2 to 6 Years

Mohammad Gharavifard[1], Arash Peivandi[2], Shahram Amini[3],
Tayebeh beygom Haji seyed Abootorabi[4], Saeed Bayyenat[5], *Alireza Sabzevari[6]

[1]Associated Professor of Anesthesiology, Department of Anesthesiology, Dr Sheikh Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.
[2]Assistant Professor of Anesthesiology, Cardiac Anesthesia Research Center, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
[3]Associate Professor of Anesthesiology, Department of Anesthesiology, Mashhad University of Medical Sciences, Mashhad, Iran.
[4]Resident of Anesthesiology, Department of Anesthesiology, Mashhad University of Medical Sciences, Mashhad, Iran.
[5]Assistant Professor of Anesthesiology, Department of Anesthesiology, Baqiyatallah University of Medical Sciences, Tehran, Iran.
[6]Assistant Professor of Anesthesiology, Surgical Oncology Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Introduction:

Hypothermia is an important complication during surgery, especially in children, and is highly associated with serious adverse outcomes. One of the preventive methods is the intraoperative administration of amino acids, which can be effective through increasing thermogenesis and stimulating energy consumption. No studies have been conducted in this regard on children; therefore, we evaluated the preventive effect of intraoperative administration of amino acid on hypothermia in children.

Materials and Methods:

Forty children, aged 2 to 6 years, who were candidates for hypospadias surgery in Dr. Sheikh Hospital, Mashhad-Iran, were divided into two groups. In the case group, 10% amino acid (2 cc/kg/h) was administered two hours before the operation, and in the control group, normal saline was given as required. All patients underwent a similar method of anesthesia. body temperature was recorded before the anesthesia, immediately after it, and every ten minutes.

Results:

The mean age and weight had no difference between the groups. Duration of patients' awakening time was (13.60 ± 4.91 min), which in the case and control groups was reported as (11.90 ± 5.27) and (15.30 ± 3.96 min), respectively ($P<0.05$).
The patients’ body temperature was higher in the case group. It was not significantly different between the groups before, and until 20 min after the start of the surgery. In the next measurements, the temperature was significantly different among the groups; the difference became more prominent as the time passed.

Conclusion:

Perioperative administration of 10% amino acid causes an increase in children’s body temperature, leading to faster awakening time of the patients.

Keywords: Amino acid therapy, General anesthesia, Hypothermia.

***Coresponding Author:** Alireza Sabzevari, MD, Assistant Professor of Anesthesiology, Surgical Oncology Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail: Sabzevaria@mums.ac.ir Received date: Apr 8, 2014 , Accepted date: May 12, 2014

Introduction

Hemorrhagic syndrome is a common problem after cardiac surgery. In the performed studies, the rate of bleeding after cardiac surgery (coronary artery bypass surgery) has been reported as 5% to 25%. When there is blood circulation in the cardiopulmonary bypass machine (CBP), due to the interaction between blood and the inner surface of the device, platelet activity is impaired and the fibrinolytic reaction is intensified, which leads to coagulation disorders. It also increases bleeding in patients, which leads to the increasing need for packed-cell transfusion and other blood products. The transfusion of blood products has various side effects such as infectious complications including transmission, viral hepatitis, hemolytic and non-hemolytic reactions, and suppression of the immune system.

Various measures can be taken to reduce the incidence of hemorrhagic syndromes including autotransfusion method and diluting blood during surgery to reduce the use of allogeneic blood products. However, after surgery and patient's admission to the intensive care unit (ICU), hemorrhage continues as mediastinal blood drainage, and leads to the increasing use of blood products, various associated complications, prolonged ICU stay, and increased mortality rate.

Since the stimulation of fibrinolysis and reduced coagulation factors such as fibrinogen may lead to mediastinal hemorrhage, in this study, we evaluated and compared the use of tranexamic acid and fibrinogen in reducing mediastinal bleeding and decreasing the administration of blood products after open heart surgery.

Materials and Methods

This study (No. 910289) was performed on 13 October 2012 after the approval of the ethics committee of Mashhad University of Medical Sciences and obtaining written informed consents from the patients in the teaching hospitals of this university.

This study was a prospective interventional clinical trial. The study population included all children referring to Dr. Sheikh Hospital in Mashhad-Iran, who were candidates for elective hypospadias surgery. The two-stage sampling method was applied; in the first stage, the eligible subjects were selected by easy non-random method and in the second stage, they were randomly assigned to two groups. Field data collection method was applied and data were gathered using checklists and observation.

The inclusion criteria were as follows: 1) American Society of Anesthesiologists class I and II (ASA); 2) 2-6 years of age; 3) candidate for hypospadias surgery; 4) absence of early coagulopathy [disorders associated with platelet count (PLT), international normalized ratio (INR), prothrombin time (PT), and partial thromboplastin time (PTT)]; 5) lack of diabetes; 6) non-consumption of Non-steroidal anti-inflammatory drugs (NSAIDS), 48 hours before surgery; 7) no excessive consumption of glucocorticoid; and 8) no need for supplemental doses of corticosteroid before anesthetic induction.

The exclusion criteria were as follows: 1) Out-of-range temperature of the operation room; 2) amino acid sensitivity; 3) operation time of more than 2.5 hours or less than 2 hours; 4) initial body temperature of $<36°C$ or $>38°C$; 5) use of sympathomimetics (ephedrine-atropine) before or during the surgery; 6) intraoperative use of heating devices; and 7) more than 20% changes in blood pressure and heart rate.

The study variables included the study group, body temperature, age, sex, bleeding, and awakening time.

The sample size was calculated according to the formula, derived from the article of

Selden and colleagues (1), with regard to the body temperature of patients in the two groups (undergoing surgery) after waking up (36.56±0.1 and 35.76±0.1, respectively). However, the mentioned study was conducted on adults and unfortunately, no other sources were available. Body temperature was similar in both groups at the start of the study.

$$n = \frac{(S_1^2 + s_2^2) \times (Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{(\bar{X}_1 - \bar{X}_2)^2}$$

$$\frac{(0.1^2 + 0.1^2) \times (1.96 + 0.84)^2}{(36.56 - 35.76)^2} \approx 1$$

The sample size calculation showed that the current study could be conducted with any sample volume to reach the desired results. However, to be certain about the outcome of the study, the sample size was considered as 20 patients in each group.

Among children, aged 2 to 6 years, who were candidates for hypospadias surgery and had referred to Dr. Sheikh Hospital, 40 cases were randomly selected. Afterwards, the patients were randomly divided into case and control groups, using the random assignment table. The basal body temperature of children in both groups was measured and recorded with a tympanic probe before serum injection.

In the study group, administration of 10% amino acid (2cc/kg/h) was started two hours before the surgery, which continued during the operation with normal saline solution (as a preservative solution). According to the formula and based on the patient's weight, the calculated amount of amino acid was deducted from the preservative solution and was continued until the end of the operation (maximum rate of amino acid was 4 cc/kg/h, and the maximum amount was 1 gr/kg). In the control group, normal saline solution was solely injected.

Fentany l 2 µg/kg, thiopental sodium 5 mg/kg, and atracurium 0.5 mg/kg were used for the patients' anesthesia and propofol 100 µg/kg/min was used for the intraoperative maintenance. After general anesthesia (GA), body temperature was measured at moment zero using the same probe.

The patients were monitored for body temperature, heart rate, blood pressure, and pulse oximetry. The patients' position was supine and routine NPO was performed.

During surgery, body temperature was recorded every 10 minutes in both groups, and the heating device was not used during the operation. The temperature of the prescribed sera was similar to the temperature of the operation room (kept at about 24°C). The measures to prevent hypothermia (including the operation room temperature, the temperature of the prescribed sera, and avoidance of wetting the body surface) were similarly taken in each group.

The rate of bleeding was recorded based on the suction volume and blood gas at the end of surgery. The patient's hematocrit was maintained at 30%; in case hematocrit was less than 30%, packed cell infusion was used. Variables were recorded until the end of the surgery and then the patients' awakening time (from the end of surgery to the first response to verbal stimulation) was recorded in both groups.
The collected data were entered into SPSS version 11.5.

Results

In the current study, the mean age of the patients was (4.17±1.64) years, which was (4.04±1.71) years in the case group and (4.29±1.60) years in the control group (P=0.630). The mean weight of the patients was (17.62±5.48) kg, which was (17.25±5.72) and (18.00±5.35) kg in the case and control groups (P= 0.630).

Duration of awakening time (from the end of surgery until the patient's waking-up) was (13.60± 4.91) min, with (11.90±5.27) and (15.30±3.96) min in the case and control groups (P= 0.027) (Table 1).

Table 1: Distribution of awakening time after surgery (in total and regarding the two groups)

Awakening time				
Group	Case group	Control group	Total	P-value
Duration	11.90±5.27	15.30±5.27	13.60±4.91	0.027

The amount of intraoperative bleeding in all patients was (34.00±16.04) mL in total, with (32.75±16.32) CC and (35.26±16.08) CC in the case and control groups, (P= 0.628) (Table 2).

Table 2: The amount of intraoperative bleeding in total and regarding the two groups

Intraoperative bleeding (CC)				
Group	Case group	Control group	Total	P-value
Amount	35.26±16.08	32.75±16.32	34.00±16.04	0.628

The patients' body temperature at base time, after the induction of anesthesia, every ten minutes until the end of operation, and immediately after waking up in both groups is indicated in the following table. As it can be seen, although the patients' body temperature was higher, before anesthesia and within the first few minutes, in the case group, the difference was not statistically significant. After 40 minutes of operation, the temperature was significantly different between the two groups; the temperature difference became even more significant as the surgery continued. T-test was used to measure body temperature at different times (Table 3) (Fig. 1).

Table 3: The patients' temperature in total and regarding the two groups at different times

Body temperature (C)				
Group	**Control group**	**Case group**	**Total**	**P-value**
Basal temperature	37.02±0.14	37.10±0.17	37.06±0.16	0.097
After induction	36.98±0.17	37.08±0.19	37.03±0.18	0.086
After 10 min of induction	36.96±0.16	37.06±0.16	37.01±0.17	0.059
After 20 min of induction	36.90±0.17	37.00±0.17	36.95±0.18	0.073
After 30 min of induction	36.83±0.20	36.91±0.18	36.87±0.19	0.19
After 40 min of induction	36.78±0.17	36.88±0.18	36.83±0.18	0.081
After 50 min of induction	36.73±0.16	36.83±0.17	36.78±0.17	0.065
After 60 min of induction	36.69±0.20	36.84±0.21	36.76±0.21	0.025
After 70 min of induction	36.65±0.21	36.80±0.22	36.73±0.23	0.034
After 80 min of induction	36.59±0.21	36.74±0.23	36.67±0.23	0.035
After 90 min of induction	36.56±0.19	36.71±0.22	36.63±0.22	0.027
After 100 min of induction	36.51±0.18	36.72±0.24	36.62±0.24	0.004
After 110 min of induction	36.48±0.17	36.71±0.24	36.59±0.24	0.002
After 120 min of induction	36.47±0.17	36.77±0.28	36.62±0.28	0.002
After 130 min of induction	36.40±0.15	36.72±0.31	36.56±0.29	0.007
After 140 min of induction	36.29±0.12	36.57±0.28	36.43±0.26	0.03
After 150 min of induction	36.19±0.20	36.30±0.35	36.39±0.31	0.03
After waking up	36.18±0.61	36.85±0.58	36.52±0.60	0.29

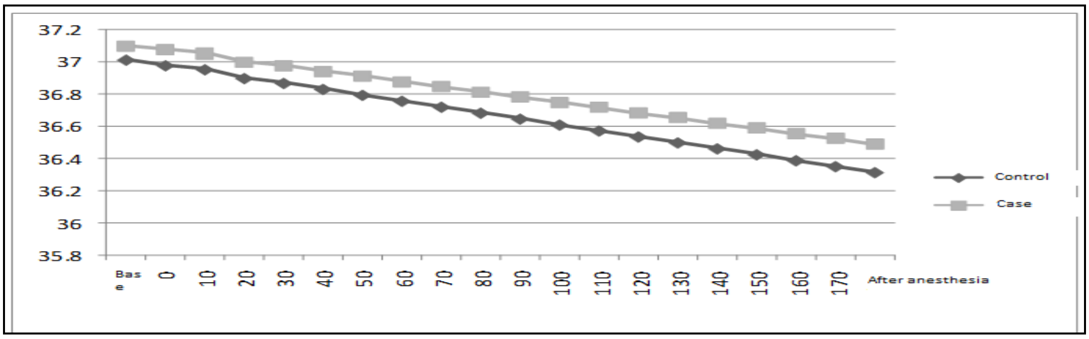

Fig. 1: The patients' body temperature

Discussion

In the current study, the length of awakening time was 13.60±4.91 min, which was 11.90±5.27 and 15.30±3.96 min in the case and control groups, respectively; there was a significant difference between the two groups. Intraoperative bleeding was 34.00±16.04 cc, which was not different between the groups.

Although the patients' body temperature was higher in the case group, the difference was not significant between the groups before, after, and 10 and 20 minutes after the start of surgery. However, this difference was significant in the next measurements and after waking up; this difference increased by time.

The effects of amino acid administration on patients' body temperature have been investigated by various researchers. In this study, the incidence of other complications such as shivering has been investigated, and the effect of amino acid administration along with different hypnotics has been compared to the effect of amino acid alone. These effects have been evaluated both in GA and epidural anesthesia (2,3) and in various surgical procedures such as open heart surgery (4). However, the analysis has not included children, which was the focus of our study.

Several studies on adults have fully examined the effects of amino acid administration on reducing shivering after surgery (5,6), decreasing intraoperative bleeding (7), improving immunologic function and accelerating wound healing (8), reducing the length of hospital stay (9), the patients' prognosis (4), and other associated complications (arrhythmias, hypertension, and myocardial ischemia) (10). In our study, we only examined the effect of amino acid administration on reducing bleeding and awakening time.

In most studies, it was shown that amino acid administration increases body temperature (11) or leads to a decrease in body temperature drop, compared to the control group (12,13); this was in consistence with the findings of our study. This effect has been rejected in only two studies (3,6), one of which included surgeries lasting more than 180 minutes (3).

The temperature drop, following amino acid administration, has been explained by patients' increased thermal threshold (10), accumulation of body temperature (7), and reduced splanchnic oxygen uptake (1). It has been shown that fat movement is inhibited by amino acid administration (2), and nitrogen production is also reduced (12) without activating stress hormones or sympathoadrenal pathway (14).

This effect has been studied in various hypnotics such as propofol along with isoflurane (11) and sevoflurane along with propofol (3), which had various effects. Therefore, in our study, we used only one anesthetic method with one single hypnotic medication. This section describes various compare their findings with those of the present study.

Selden et al, stated that amino acid infusion stimulates energy production and heat accumulation in healthy individuals. Results showed the measured temperature drop and oxygen uptake were higher in the control group compared to the group receiving amino acids. It was concluded that the patients after the end of anesthesia did not experience shivering and immediately regained the normal temperature by amino acid administeration (5). We also observed a similar temperature change in our study, however, shivering was not studied .

The same researcher, two years later in 1996, studied the effect of the stimulation of energy production by amino acid infusion during surgery; prevention of hypothermia was also studied based on the rate of gas exchange and rectal temperature. It was concluded that amino acid infusion during anesthesia prevents hypothermia through heat accumulation and delayed heat stimulation; the findings were similar to the results of our study (regarding adult subjects) (1).

In other studies, the effect of amino acid infusion during general anesthesia on nitrogen excretion after surgery was investigated; these results, could justify the findings of our study on children(12,14).

The results related to the patients' temperature and length of stay Sellden’s study in 1999, was similar to the researcher’s previous study and consistent with our findings; this suggests that the effect of amino acid is similar in children and adults (12).

Selden et al, in another study in 2001 investigated the cause of dysfunction in temperature central sensors, which is amplified by the thermogenic effect of amino acids. GA causes hypothermia by reducing the metabolic rate and defects in the patient's thermoregulation. There are studies conducted in this field, and we many recommendations to prevent heat loss. However, little attention has been paid to the stimulation of heat production by the patient. Nutrient-induced thermogenesis can be seen in all nutrients, and the highest thermic effect is found in amino acid solution (about 30-40%). This effect increases during anesthesia, when the function of temperature central sensors is impaired, and the thermogenesis effect of amino acid is intensified, which can prevent hypothermia (15). This indicates the benefit of this drug, which inhibits body temperature drop without increasing these hormones.

In the study of Sahin et al, conducted at the Department of Anesthesiology in Turkey, Ankara, in 2002, the preventive effects of amino acid on hypothermia and shivering under different anesthetics were compared. Results showed that amino acid administration during general anesthesia improves body temperature; its effect is more significant with propofol compared to isoflurane (11). In our study, we only used one type of hypnotic medication, but the findings related to thermal pattern were similar in the two studies.

Chandraskaran et al, in 2005, conducted a study with the aim to demonstrate that the administeration of amino acid infusion during GA can prevent postoperative hypothermia. Results showed body temperature increased during recovery time, following the infusion of amino acids (16); this is in consistence with the findings of our study on children.

Kamitany et al, in 2005 concluded that sevoflurane was more effective in preventing hypothermia, compared to propofol, in the group receiving amino acids (17). The findings were similar to our study, although the effects of different hypnotics were not examined in the current study.

Yamaoka et al, in 2006, showed that the administration of amino acids under general anesthesia stimulates protein synthesis in muscles and helps with the accumulation of body temperature. Also, the infusion of amino acids during surgery is effective in reducing intraoperative bleeding (7); in our study, amino acid administration was not associated with reduced bleeding.

In a study performed by Mizobe et al, heat production increased after infusion or receiving nutrients, which is related to the thermogenesis effect of nutrients. The thermogenesis effect of protein or amino acid lasts longer and is quite well established. Considering this physiological effect, the preoperative administration of amino acid can prevent hypothermia during GA and spinal anesthesia. It was shown that amino acid infusion increases core body temperature threshold for the required vasoconstriction to regulate the temperature; it also increases energy consumption. It was also reported that the administration of amino acids in time of off-pump coronary artery bypass grafting (OPCAB) improves the outcomes (18), which is in consistence with the findings of our study.

Zhong et al, in 2010, evaluated the effect of amino acid infusion on lipid metabolism and body temperature during gastrointestinal surgery. Results showed that amino acid infusion could prevent hypothermia during and 2 h after surgery and inhibit lipid motion (2). The patients' body temperature pattern in this study was similar to the pattern in our study. Inoue et al, in 2011 found that amino acid infusion after the spread of hypothermia did not lead to a re-increase of temperature; however, it decreased postoperative shivering. Thus, it can be concluded that the start of amino acid infusion after hypothermia spread does not influence re-warming. This finding was similar to that of Kamitany's study (on the surgery lasting more than 180 min) (3), but was inconsistent with the results of the current study and other research; however, amino acid infusion can prevent postoperative shivering (6).

Conclusion

Perioperative administration of 10% amino acid decreases children's body temperature during and after surgery. This decrease in temperature leads to a faster awakening of patients after surgery.

Acknowledgment

We appreciate the Research Council of Mashhad University of Medical Sciences and the personnel of affiliated teaching hospitals, who helped us with performing this study.

References

1. Sellden E, Branstorm R, Brundin T. Preoperative Infusion Of Amino Acids Prevents Postoperative Hypothermia. BrJAnaesth 1996;76(10):227-34.
2. ZHONG J, Sheng-jin G, ZHUANG X, CANG J, Zhang-gang X. Effect of intraoperative amino acids infusion on the metabolism of fat and body temperature in the patients undergoing gastrointestinal surgery. Anesthesia 2011;04(11):101.
3. Kamitani K, Yoshida H, Takagi M, Minami M, Tokutake M, Kishi R, et al. [Effect of amino acid infusion for prevention of intraoperative hypothermia during laparotomy]. Masui The Japanese journal of anesthesiology 2006 Oct;55(10):1216-21.
4. Moriyama T, Tsuneyoshi I, Omae T, Takeyama M, Kanmura Y. The effect of amino-acid infusion during off-pump coronary arterial bypass surgery on thermogenic and hormonal regulation. Journal of anesthesia. 2008;22(4):354-60.
5. Sellden E, Brundin T, Wahren J. Augmented thermic effect of amino acids under general anaesthesia: a mechanism useful for prevention of anaesthesia-induced hypothermia. Clinical science 1994 May;86(5):611-8.

6. Inoue S, Shinjo T, Kawaguchi M, Nakajima Y, Furuya H. 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: a randomized trial. Journal of anesthesia 2011 Dec;25(6):850-4.
7. Yamaoka I, Doi M, Nakayama M, Ozeki A, Mochizuki S, Sugahara K, et al. Intravenous administration of amino acids during anesthesia stimulates muscle protein synthesis and heat accumulation in the body. American journal of physiology Endocrinology and metabolism. 2006 May;290(5):E882-8.
8.Sellden E. Peri-operative amino acid administration and the metabolic response to surgery. The Proceedings of the Nutrition Society. 2002 Aug;61(3):337-43.
9. Sellden E, Lindahl SG. Amino acid-induced thermogenesis reduces hypothermia during anesthesia and shortens hospital stay. Anesth Analg 1999 Dec;89(6):1551-6.
10. 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]. Vojnosanitetski pregled Military-medical and pharmaceutical review. 2007 Jun;64(6):421-4.
11.Sahin A, Aypar U. Effect of amino acid solutions on intraoperative hypothermia and postoperative shivering. Comparison of two anesthetic regimens. Acta anaesthesiologica Scandinavica 2002 Jan;46(1):64-7.
12.Sellden E, Lindahl SG. Postoperative nitrogen excretion after amino acid-induced thermogenesis under anesthesia. Anesth Analg 1998 Sep;87(3):641-6.
13. Sellden E, Sten GE, Lindahl. Amino Acid-Induced Thermogenesis Reduces Hypothermia During Anesthesia and Shortens Hospital Stay. Anesth Analg 1999;89(10):1551-6.
14.Sellden E, Lindahl SG .Amino acid-induced thermogenesis to prevent hypothermia during anesthesia is not associated with increased stress response. Anesth Analg 1998 Sep;87(3):637-40.
15.Sellden E. [Amino acid administration counteracts hypothermia during anesthesia]. Lakartidningen 2001 Apr 4;98(14):1664-9.
16. Chandrasekaran TV, Morgan RN, Mason RA, Mangat PS, Watkins AJ, Carr ND . Nutrient induced thermogenesis during major colorectal excision--a pilot study. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 2005 Jan;7(1):74-8.
17. Kamitani K, Higuchi A, Nohara A, Takagi M, Tokutake M, Horikawa H, et al. [Effect of amino acid solution on intraoperative core temperature the influence of anesthetics]. Masui The Japanese journal of anesthesiology. 2005 Nov;54(11):1258-62.
18.Mizobe T, Nakajima Y. [Dietary-induced thermogenesis and perioperative thermo-regulation]. Masui The Japanese journal of anesthesiology 2007 Mar;56(3):305-16.