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ORIGINAL ARTICLE

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

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Abstract
Purpose Previous studies have demonstrated that amino acid infusions exert enhanced thermogenic effects during general anesthesia. This study was conducted to investigate whether amino acid infusions started after development of intraoperative core hypothermia can accelerate rewarming.
Methods Twenty-two patients scheduled for major abdominal surgery were included in this study. When tympanic temperature reached 35.5°C, patients were randomly assigned to receive amino acids (amino acid group; $n = 11$) or saline (saline group; $n = 11$). A continuous infusion of a mixture of 18 amino acids or saline was started at 200 ml h^{-1}. Tympanic, forearm, and digit temperatures were recorded. Forearm minus fingertip skin-surface temperature gradients (temperature gradient) were calculated. Postoperative shivering was also evaluated.
Results Tympanic membrane temperature and temperature gradient were similar between the two groups at each time point during the study period. Temperature gradient at extubation in the amino acid group was significantly lower than in the saline group although tympanic temperature at extubation was similar between the two groups. Postoperative shivering score was significantly lower in the amino acid group than in the saline group.
Conclusions Amino acid infusions started after development of intraoperative core hypothermia failed to accelerate rewarming. However, amino acid infusions reduced the incidence of postoperative shivering. Use of amino acid infusions to reduce thermoregulatory vasoconstriction at emergence might contribute to a decrease in the development of postoperative shivering.

Keywords Amino acid · Hypothermia · Shivering

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Introduction

It has been suggested that intraoperative hypothermia adversely affects postoperative outcomes [1–4]. Inadvertent perioperative hypothermia is associated with coagulopathy and increased allogeneic transfusion requirement [1], surgical wound infection and prolonged hospitalization [2], delayed postanesthetic recovery [3], and morbid cardiac complications [4]. Therefore, it is conceivable that inadvertent perioperative hypothermia should be appropriately restored to normothermia as soon as possible. Previous studies have demonstrated that amino acid infusions exert enhanced thermogenic effects during general anesthesia [5]. However, it has been reported that amino acid infusions started at the commencement of anesthesia do not prevent the initial reduction in temperature [5].

Core hypothermia during general anesthesia develops with three characteristic phases [6–8]. Initial core hypothermia results from core-to-peripheral redistribution of body heat when anesthesia inhibits tonic thermoregulatory vasoconstriction. Subsequently, heat loss exceeding metabolic heat production reduces core temperature in a slow, linear fashion. Finally, a core temperature plateau results when emergence of thermoregulatory vasoconstriction decreases cutaneous heat loss and constrains metabolic heat to the core thermal compartment.

Considering development of core hypothermia through these characteristic phases, it might be difficult to prevent initial core hypothermia by use of amino acid infusions during induction of anesthesia, because of massive heat loss which far exceeds the thermogeneration induced by amino acid infusions. However, thermogeneration induced by amino acid infusions can be effectively maintained at a core temperature plateau phase after initial core hypothermia, which might result in increasing heat accumulation. For that reason, this study was conducted to investigate whether amino acid infusions started after development of intraoperative core hypothermia can accelerate rewarming.

Methods and materials

This study was performed as a randomized controlled trial in accordance with the recommendations of the CONSORT consensus statement [9]. Ethical approval for this study (Ethical Committee no. 04-027) was obtained from the Ethical Committee of Nara Medical University Hospitals, Nara, Japan (Chairperson Professor S. Nakamura) on October 31st 2006. This study was conducted between November 1st 2006 and December 31st 2007. Thirty eight patients scheduled for major abdominal surgery were eligible. Six patients with symptomatic ischemic heart disease, hepatic or renal disease, or coagulopathy were excluded. In addition, 10 patients who were administered vasodilator medications were excluded. At the commencement of the study, it was intended that patients with a tympanic temperature greater than 37.5°C or less than 36.5°C would be excluded; however, none was excluded. Finally, 22 patients were enrolled.

The standard institutional anesthetic practice for major abdominal surgery, which includes a variety of methods for maintaining normothermia, was modified to enable development of intraoperative core hypothermia in this study. No patients were premedicated. On arrival in the operating room, routine monitoring was applied, including electrocardiography, noninvasive blood pressure, pulse oximetry, and capnography. A tympanic membrane probe was inserted in the right external auditory meatus for core temperature monitoring by use of sterile copper-constantan thermocouple sensors (Mallinkrodt Medical, St Louis, MO, USA). The probe was then taped in place, the aural canal occluded with cotton, and the external ear covered with a gauze pad. Skin-temperature probes equipped with adhesive (Mallinkrodt Medical) were placed on the surface of the forearm and the index fingertip. A 20-gauge catheter was inserted into the forearm vein for fluid and drug administration. Acetate Ringer's solution at room temperature was administered at 500 ml/h during surgery. However, infusion rates were changed depending on situations. Ambient temperature was maintained at approximately 23–24°C. Before induction of anesthesia, an epidural catheter was inserted at the 8–9 or 9–10th thoracic interspace and placed 5 cm beyond the introducer needle tip. Three milliliters of epinephrine-containing (1:100,000) 1% lidocaine was used to detect unintentional intravascular or intrathecal catheter placement, which was followed by continuous infusion of 0.375% ropivacaine at 5 ml/h. Anesthesia was induced with propofol 1.5–2.5 mg/kg, fentanyl 1–2 μg/kg, and vecuronium 0.1 mg/kg. Anesthesia was maintained with 3% end-tidal sevoflurane in oxygen until tracheal intubation. Anesthesia was then maintained with 2% end-tidal sevoflurane in 40% oxygen (air/oxygen mixture at 4 l/min), supplemented with doses of fentanyl and vecuronium. A heat and moisture-exchanging filter was positioned between the endotracheal tube and the breathing circuit. Patients were covered with a single cotton blanket during the study period.

Tympanic, forearm, and digit temperatures were recorded just before (Time 0) and every 15 min for 4 h after induction of anesthesia. Forearm minus fingertip skin-surface temperature gradients (temperature gradient) were also calculated and recorded. The gradients were recorded from an arm not having an intravenous cannula or blood pressure cuff. As in the previous study, we considered a temperature gradient >0°C to indicate vasoconstriction [10]. When tympanic temperature decreased to 35.5°C, patients were randomly assigned to receive amino acids (amino acid group; $n = 11$) or saline (saline group; $n = 11$). Sealed envelopes were used for group assignment. Attending anesthesiologists were blinded to the test drugs. A continuous infusion of a mixture of 18 amino acids (Amiparen®; Otsuka Pharmaceutical, Tokyo, Japan) or saline was started at 200 ml h^{-1}, using a syringe pump (Terufusor, TE-312; Terumo, Tokyo, Japan). The infusion was continued for 1 h. Simultaneously, patients received intraoperative forced air warming using an upper body blanket (Bair Hugger Blanket; Augustine Medical, Eden Prairie, MN, USA) over the single cotton blanket. The Bair Hugger Model 500 Warming Unit (Augustine Medical) was connected to the blanket using the medium temperature setting (38°C). The arm used to monitor the skin temperature was excluded from the forced-air cover. After the operation, the tracheal tube was removed when tympanic temperature reached more than 36°C. Tympanic temperature and temperature gradient at extubation were recorded. Patients who fulfilled a standard criterion (a modified Aldrete score >9) [11] were transported directly from the operating room to the surgical ward recovery area. Postoperative shivering was evaluated by observers blinded to group assignment and was scored as none, mild, moderate, or severe upon arrival in the surgical ward recovery area [12].

Table 1 Patient characteristics and intraoperative variables

	Amino acid group ($n = 11$)	Saline group ($n = 10$)	P value
Age (year)	66 ± 7	66 ± 8	0.8501
Sex (M/F)	7/4	7/3	0.9999
Height (cm)	159 ± 8	162 ± 10	0.3733
Body weight (kg)	63 ± 8	66 ± 10	0.3587
Anesthesia time (min)	411 ± 28	428 ± 30	0.1788
Operation time (min)	332 ± 30	346 ± 31	0.3114
Infusion (ml)	3323 ± 475	3638 ± 653	0.2179
Transfusion (ml)	133 ± 316	219 ± 494	0.6357
Urine (ml)	750 ± 114	789 ± 114	0.4461
Blood loss (ml)	556 ± 354	636 ± 416	0.6408
Fentanyl used during anesthesia (μg)	325 ± 54	327 ± 47	0.9187
Tympanic temperature at extubation (°C)	36.3 ± 0.3	36.3 ± 0.2	0.6197
Temperature gradient at extubation (°C)	0.2 ± 0.9	1.6 ± 1.6	0.0118[a]

[a] The average temperature gradient at extubation was significant lower in the amino acid group than in the saline group

Statistical analysis

The study population size was determined on the basis of the following hypothesis. We arbitrarily assumed that amino acid infusions can restore core temperature at 0.5°C higher than saline 4 h after anesthesia induction. Based on the formula for normal theory and assuming a type I error protection of 0.05 and a power of 0.8, 9 patients in each group were required. Thus, we employed 11 patients in each group for the study population size.

Comparisons of changes in temperature between the groups were performed by analysis of variance for repeated measures. Other comparisons between the groups were carried out by using Student's t test for continuous variables, Mann–Whitney's U test for nonparametric data, and the chi-squared test for nominal data. The data are expressed as mean ± standard deviation of the mean (SD); differences were considered significant when $P < 0.05$.

Results

Because of failure to obtain temperature data, 1 patient in the saline group was excluded from the study. Patient characteristics including intraoperative variables are shown in Table 1. These values were comparable between the two groups. Intraoperative changes in tympanic membrane temperature and temperature gradient are presented in Figs. 1 and 2. Both tympanic membrane temperature and temperature gradient were similar between the two groups at each time point during the study period (of 4 h after induction of anesthesia). The average temperature gradient at extubation was significantly lower in the amino acid group than in the saline group although tympanic temperatures at extubation were similar between the two groups.

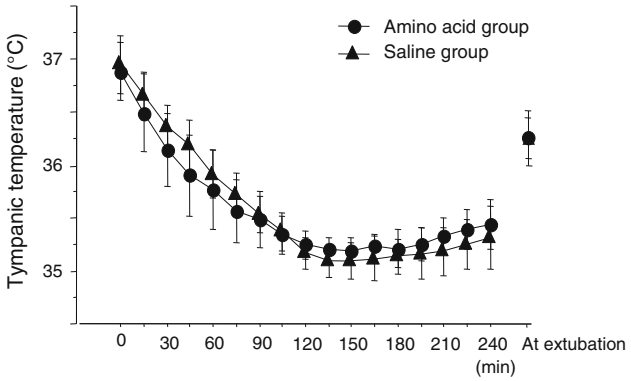

Fig. 1 Changes in tympanic temperature The data are expressed as mean ± standard deviation (SD). Time 0 is just before induction of anesthesia. At extubation is when the patient's trachea was extubated

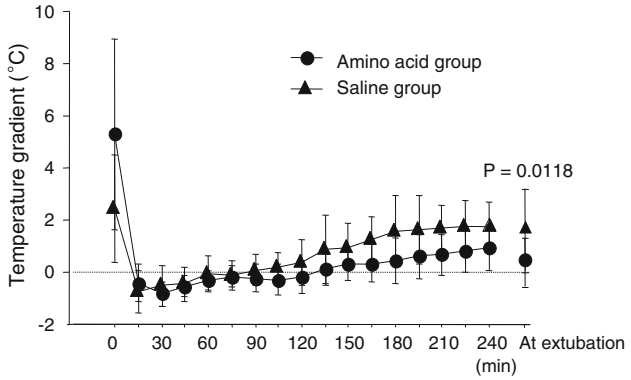

Fig. 2 Changes in forearm minus fingertip skin-surface temperature gradient (temperature gradient). Data are expressed as mean ± standard deviation (SD). Time 0 is just before induction of anesthesia. At extubation is when the patient's trachea was extubated. The average temperature gradient at extubation was significantly lower in the amino acid group than in the saline group

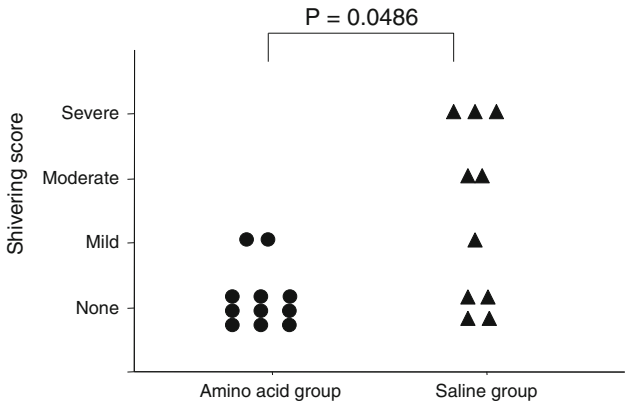

Fig. 3 Postoperative shivering score. The postoperative shivering score was significantly lower in the amino acid group than in the saline group

The postoperative shivering score was significantly lower in the amino acid group than in the saline group (Fig. 3).

Discussion

The results in this study revealed that amino acid infusions started after the development of intraoperative core hypothermia did not affect rewarming but reduced the incidence and severity of postoperative shivering. Although tympanic temperatures changed similarly after amino acid infusion, forearm minus fingertip skin-surface temperature gradient (temperature gradient) at extubation was significantly lower in the amino acid group than in the saline group. These results suggest that amino acid infusions resulted in decreased thermoregulatory vasoconstriction at emergence and this effect might contribute to the decrease in the development of postoperative shivering.

As already mentioned, it has been demonstrated that amino acid infusions exert enhanced thermogenic effects during general anesthesia [5]. The mechanism behind this phenomenon is not fully understood, although nutrient intake stimulates energy expenditure, and hence heat production [13]. Amino acid infusions have resulted in providing patients with the beneficial outcome that, on emergence from anesthesia, they were normothermic and free from shivering [5, 13–15]. However, it has been pointed out that amino acid infusions cannot effectively prevent initial hypothermia after general anesthesia [5, 14].

After rapid initial core hypothermia during anesthesia induction, which results from inhibition of tonic thermoregulatory vasoconstriction, a core temperature plateau occurs because of emergence of thermoregulatory vasoconstriction, in which cutaneous heat loss and metabolic heat production are in balance [6–8]. Therefore, failure of effective prevention of hypothermia by amino acid infusions at the commencement of anesthesia is probably because heat loss by redistribution of body heat is much greater than thermogenesis by amino acids during induction of anesthesia. This interpretation might suggest that thermogenesis by amino acids can be used more effectively during the core temperature plateau phase after redistribution of body heat rather than before or during redistribution of body heat.

Contrary to our hypothesis, amino acid infusions started after development of intraoperative core hypothermia were not able to accelerate rewarming. A lower metabolic capacity with concomitant reduction of core body temperatures might be insufficient to produce effective thermogenesis by amino acid infusions that was expected to counteract core hypothermia [16]. However, it is supposed that thermogenesis by amino acids did occur to some extent because the temperature gradient at extubation was smaller in the amino acid group. Temperature gradient indicates the status of thermoregulatory vascular tone [10]. Therefore, thermogenesis by amino acids, which, however, did not affect core temperature, is considered to have reduced thermoregulatory vasoconstriction. Additionally, one report showed negative results regarding intraoperative rewarming by amino acid administration started after induction of anesthesia but positive results regarding postoperative rewarming [17]. If intensive postoperative observation had been conducted in our study, similar results might have been obtained.

The reason why amino acid infusions reduced the development of postoperative shivering is probably because the degree of thermoregulatory vasoconstriction at emergence was milder in the amino acid group. Decrease in thermoregulatory vasoconstriction is indicated by an increase in peripheral temperatures. Peripheral temperature is an important predictor of postoperative shivering [18, 19]. Cheng and co-workers demonstrated that peripheral and core temperature contribute linearly to the control of shivering and that peripheral temperature contributed approximately 20% to shivering [18]. Therefore, decrease in skin temperature linearly increases core temperature threshold for shivering, i.e., patients with low skin temperature are more likely to shiver. Collectively, patients in the amino acid group might not have required heat production by shivering to maintain normothermia at emergence from anesthesia because of presence of thermogenesis by amino acid infusions.

We did not measure energy expenditure or nitrogen balance during perioperative periods. Therefore, we cannot quantify the effects of amino acid infusions on hypothermic status. This might be a limitation of this study; however, this study provides beneficial information to deal with postoperative shivering due to inadvertent perioperative hypothermia. The issue might be raised that the epidural

injection of local anesthetic could have affected the results of this study. However, it was used equally for all patients. Therefore, it is reasonable to suppose that this issue hardly worked as a bias of the study. Previous reports used below 35°C as a definition of intraoperative hypothermia [1–4]. According to our clinical experience, we know that body temperature usually drifts downward to approximately 35°C, as shown in Fig. 1. Thus, we used 35.5°C as the starting point for amino acid infusion. Regarding the amino acid product we used, previous Japanese studies focusing on a topic of amino acid infusion and intraoperative body temperature have used the same commercial product (Amiparen®) [20, 21]. In addition, they obtained positive results. Accordingly, we used this solution. One of these studies used an infusion rate of 200 ml/h [21]. Therefore, we used the same infusion rate. There might be a concern that pain after recovery from anesthesia can cause postoperative shivering. There was no significant difference in supplemented doses of fentanyl required during anesthesia between the groups and the doses were not large. Therefore, it is reasonable to consider that epidural analgesia for both groups were equally effective. Hemodynamic status during surgery was also similar (data not shown). Thus, it is not logical to suppose that difference of pain intensity significantly affected the study results.

In conclusion, amino acid infusions failed to accelerate rewarming after development of intraoperative core hypothermia. However, amino acid infusions reduced the incidence and severity of postoperative shivering. Reduced thermoregulatory vasoconstriction on emergence from anaesthesia, which was considered to be induced by thermogenesis by amino acids, probably contributed to the decrease in the incidence and severity of postoperative shivering.

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References

1. Schmied H, Kurz A, Sessler DI, Kozek S, Reiter A. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. Lancet. 1996;347:289–92.
2. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization Study of Wound Infection and Temperature Group. N Engl J Med. 1996;334:1209–15.
3. Lenhardt R, Marker E, Goll V, Tschernich H, Kurz A, Sessler DI, Narzt E, Lackner F. Mild intraoperative hypothermia prolongs postanesthetic recovery. Anesthesiology. 1997;87:1318–23.
4. Frank SM, Fleisher LA, Breslow MJ, Higgins MS, Olson KF, Kelly S, Beattie C. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial. JAMA. 1997;277:1127–34.
5. Selldén E, Brundin T, Wahren J. Augmented thermic effect of amino acids under general anaesthesia: a mechanism useful for prevention of anaesthesia-induced hypothermia. Clin Sci (Lond). 1994;86:611–8.
6. Sessler DI, McGuyre J, Moayeri A, Hynson J. Isoflurane-induced vasodilation minimally increases cutaneous heat loss. Anesthesiology. 1991;74:226–32.
7. Matsukawa T, Sessler DI, Sessler AM, Schroeder M, Ozaki M, Kurz A, Cheng C. Heat flow and distribution during induction of general anesthesia. Anesthesiology. 1995;82:662–73.
8. Hynson J, Sessler DI. Intraoperative warming therapies: a comparison of three devices. J Clin Anesth. 1992;4:194–9.
9. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001;357:1191–4.
10. Kurz A, Sessler DI, Birnbauer F, Illievich UM, Spiss CK. Thermoregulatory vasoconstriction impairs active core cooling. Anesthesiology. 1995;82:870–6.
11. Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth. 1995;7:89–91.
12. Baker KZ, Young WL, Stone JG, Kader A, Baker CJ, Solomon RA. Deliberate mild intraoperative hypothermia for craniotomy. Anesthesiology. 1994;81:361–7.
13. Jéquier E. The influence of nutrient administration on energy expenditure in man. Clin Nutr. 1986;5:181–6.
14. Selldén E, Bränström R, Brundin T. Pre-operative infusion of amino acids prevents postoperative hypothermia. Br J Anaesth. 1996;96:227–34.
15. Selldén E, Bränström R, Brundin T. Augmented thermic effect of amino acids under general anaesthesia occurs mainly in extrasplanchnic tissues. Clin Sci. 1996;91:431–9.
16. Selldén E, Lindahl SGE. Postoperative nitrogen excretion after amino acid-induced thermogenesis under anesthesia. Anesth Analg. 1998;97:641–6.
17. Chandrasekaran TV, Morgan RN, Mason RA, Mangat PS, Watkins AJ, Carr ND. Nutrient induced thermogenesis during major colorectal excision—a pilot study. Colorectal Dis. 2005;7:74–8.
18. Cheng C, Matsukawa T, Sessler DI, Ozaki M, Kurz A, Merrifield B, Lin H, Olofsson P. Increasing mean skin temperature linearly reduces the core-temperature thresholds for vasoconstriction and shivering thresholds in humans. Anesthesiology. 1995;82:1160–8.
19. Nishimura C, Kanemaru K, Otagiri T. Characteristic changes between core and peripheral surface temperature related with postanesthetic shivering following surgical operations. J Anesth. 1990;4:350–7.
20. Saitoh Y, Kaneda K, Tokunaga Y, Murakawa M. Infusion of amino acid enriched solution hastens recovery from neuromuscular block caused by vecuronium. Br J Anaesth. 2001;86:814–21.
21. 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. J Anesth. 2008;22:354–60.