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Novamin infusion: a new method to cure postoperative shivering with hypothermia

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ABSTRACT

Background: Postoperative shivering is a frequent complication of surgery in developing countries and there is no satisfying method to treat it, let alone to cure it. We studied whether intravenous amino acid (AA) infusion can cure postoperative shivering in the postanesthesia care unit.

Methods: Sixty postanesthesia care unit patients with shivering grade 2 or higher and tympanic temperature <36°C received randomly either infusion of Novamin 18 AAs (2 mL/kg/h), pethidine (0.5 mg/kg), or tramadol (1 mg/kg). Tympanic temperature, shivering grade, and thermal comfort were assessed every 5 min for 60 min. Blood glucose and lactic acid concentrations were measured before and after treatment. Postoperative nausea and vomiting were also recorded.

Results: Shivering stopped within 5 min in the pethidine and tramadol groups *versus* 90% stopped within 15 min in AA group. There were five cases of reshivering in the tramadol group *versus* none in the AA or pethidine groups. Tympanic temperature increased slowly in all patients but increased significantly faster in the AA group. Thermal comfort improved significantly faster in the AA group *versus* the other two groups, thermal comfort was significantly higher in the tramadol *versus* the pethidine group ≥35 min. Blood glucose concentration in AA group increased to 135.18 ± 9.18 mg/dL. There were some cases of nausea and vomiting in pethidine and tramadol groups but none in the AA group.

Conclusion: Novamin infusion can stop postoperative shivering and alleviates hypothermia and improves thermal comfort more effectively than tramadol and pethidine with less nausea and vomiting and causes a clinically acceptable blood glucose increase with no reshivering episodes.

This work is attributed to Department of Anesthesia, Zhongshan Hospital, Fudan University, Shanghai, China.
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1. Introduction

Postoperative shivering incidence in patients recovering from general anesthesia has been estimated to be as high as 50%–60% before several methods have been taken to maintain intraoperative normothermia in recent years [1]. However, postoperative shivering is also a frequent complication of surgery in developing countries lacking enough money to maintain normothermia, and the overwhelming majority of cases present with a core temperature <36°C [2]. Postoperative shivering is not only subjectively uncomfortable but is also physiologically stressful and harmful [2–4]. Previous research [4] revealed that a mild shivering reaction can be elicited within minutes and can rapidly progress to severe shivering involving generalized movement of all muscle groups. Therefore, once shivering is detected, timely treatment is imperative to avoid deleterious effects.

Shivering may happen as a thermoregulatory response to hypothermia [2]. However, most drugs that reduce postoperative shivering have limited capability to alleviate underlying hypothermia and instead impair thermoregulatory defenses [5,6]. The opiates pethidine (meperidine HCl) and tramadol are the most widely used antishivering drugs in clinical practice. They decrease both the vasoconstriction and shivering thresholds, which is consistent with their antishivering effect, but have the side effect of decreasing thermoregulatory control precision by reducing set points [5,6]. Thus, these drugs may be more suitable for intentionally facilitating mild therapeutic hypothermia rather than treating/curing hypothermia-induced postoperative shivering. In addition, these drugs are associated with a high incidence of nausea and vomiting. Pethidine also enhances relevant postoperative complications such as lethargy and respiratory depression [7]. Therefore, thermogenic drugs that alleviate hypothermia and shivering without compromising thermoregulatory defenses or causing serious side effects are of considerable clinical interest.

Over the past several years, we have found that intraoperative infusion of an 18-amino acid (AA)–compounded solution (Novamin 18AA-II, 11.4%) alleviated hypothermia during surgery in patients under general anesthesia combined with epidural block [8]. This treatment also had dose-dependent effects of increasing blood glucose and inhibiting fat mobilization and muscle protein breakdown in mongrel dogs [9].

AA infusion stimulates heat production and also provides nutritive substrates for shivering muscles [10]. We hypothesized that AA infusion can effectively treat postoperative shivering. Earlier studies involving one of our team administered AAs according to patient basal metabolic rate, at an infusion rate of approximately 4 kJ·kg/h, and revealed a significant favorable effect of negating intraoperative hypothermia [11], whereas Sahin and Aypar [12], who used a much lower infusion rate, 100 kJ/h (i.e., 1.3–1.7 kJ/kg/h), had negative results. Our recent study of AA infusion in dogs supported the rationale for adjusting intraoperative AA infusion rate according to patient-specific basal metabolism [9]. Seifi *et al.* [13] showed that pethidine 0.5 mg/kg was as effective as tramadol 1 mg/kg for treating postoperative shivering. Therefore, we compared the effects of Novamin infusion at 4 kJ/kg/h, pethidine 0.5 mg/kg, and tramadol 1 mg/kg on postoperative shivering with hypothermia in the postanesthesia care unit (PACU).

2. Methods

This study was approved (#B2012-091) by the Ethical Committee on Human Experiments, Zhongshan Hospital, Fudan University, Shanghai, China. Before enrollment, written informed consent was obtained from all patients. Inclusion criteria were patients of both genders, aged 20–59 y, American Society of Anesthesiologists (ASA) physical status I or II, who underwent gastrointestinal surgery under general anesthesia combined with epidural block. Patients with heart disease, respiratory insufficiency, diabetes mellitus, psychiatric, thyroid or neuromuscular disorders, history of convulsions, multiple allergies, and preoperative tympanic temperature >38°C or <36.5°C were excluded. Baseline preoperative tympanic temperature was noted in all patients. A 14F catheter was inserted as routine into the right internal jugular vein before the operation.

During postoperative recovery in the PACU, all patients were continuously monitored, received oxygen 5 L/min via a facemask and were covered with a blanket. All patients had already been giving morphine 2 mg via the epidural catheter during the operation for relief of postoperative pain and received intravenous tropisetron (6 mg) as an antiemetic before wound closure. Just after operation, all patients had patient-controlled epidural analgesia with 0.12% bupivacaine and fentanyl 2 μg/mL, 2.5 mL/h, bolus 4 mL, and lockout time 10 min. Patients who showed shivering grade 2 or higher for >3 min and tympanic temperature <36°C were randomly allocated by computer-coded envelopes into three groups ($n = 20$ patients per group) to receive either intravenous AAs (Novamin 18AA-II, lot #86901415000329; Sino-Swed Pharmaceutical Co Ltd, Wuxi, China; 2 mL/kg/h, see Appendix for complete formulation), pethidine (0.5 mg/kg), or tramadol (1 mg/kg). To double-blind the study, drug administration was separated into two steps: 2 mL normal saline was given to the AA group, followed by Novamin 18AA-II infusion at a rate of 2 mL/kg/h (approximately 4 kJ/kg/h) for 1 h via a Graseby 3500 syringe pump (SIMS Graseby Ltd, Watford, UK). Two milliliters normal saline containing either 0.5 mg/kg pethidine (Renfu Pharmaceutical Co, Ltd, Yichang, China) or 1 mg/kg tramadol (Xinghua Pharmaceutical Co, Ltd, Hubei, China) was administered to the respective pethidine or tramadol group, followed by normal saline infusion at the same rate of 2 mL/kg/h for 1 h via syringe pump. All drugs were administered via the central venous catheter. Blood samples were collected from a radial artery catheter.

Treatment drugs were all prepared by a single anesthesia nurse and other investigators were blinded to medication administered. All preloading fluids and drugs were used at room temperature. The temperature of the recovery room was maintained at 21°C–23°C with room humidity at 55%–65%.

2.1. Measurements

Shivering grades, core temperature, and thermal comfort were measured and recorded at 5-min intervals for 1 h in the PACU. Shivering grade scale was measured as follows: grade 0, no shivering; grade 1, mild neck or face fasciculation or electrocardiogram disturbances in the absence of voluntary arm activity; grade 2, visible tremors involving than one muscle group; and grade 3, gross muscular activity involving the entire body and bed shaking. Reshivering was noted until the patient left the PACU; patients having a second shivering attack grade 2 or higher were given a rescue bolus of 20 mg intravenous pethidine.

Core temperature was monitored with an infrared tympanic thermometer (ThermoScan IRT 3020; Braun, Kronberg, Germany) immediately after arrival in the PACU, and every 5 min after drug administration, for a total of 1 h. We measured bilateral tympanic temperature and the highest temperature was recorded as the true value [14]. Thermal comfort was evaluated at 5 min intervals with a 100-mm long visual analog scale (VAS), on which 0 mm was defined as the worst imaginable cold, 50 mm as thermoneutrality, and 100 mm as the worst imaginable heat. Postoperative pain was assessed using a 0–10 cm VAS, where 0 = no pain and 10 = the worst pain imaginable. Pain was treated with a bolus of patient-controlled analgesia when the reported VAS was ≥3.

Blood glucose and lactic acid concentrations were measured at the onset of treatment and 1 h later. Any reported nausea and/or observed vomiting during the 1-h recovery period was documented. Nausea or vomiting in 5 min was recorded as once.

2.2. Sample size and statistical analysis

The primary outcome measure was shivering grade, and the secondary outcome measures were tympanic temperature, thermal comfort, reshivering incidence, blood glucose and lactic acid concentrations, visual pain score, and nausea/vomiting.

To detect a 60% difference in the postoperative shivering response rate (cessation rate at 10 min) among the test groups, with a minimum response rate of 20% estimated from initial pilot observations, with 90% power and 5% alpha error (two tailed), power analysis indicated that a study population of 16 patients per group was sufficient for statistical assessment [7,15]. According to previous studies [16], the standard deviation of body temperature is approximately 0.2°C and the expected difference among groups was approximately 0.5°C, so five patients per group were calculated to be sufficient (90% power and 5% alpha error). Thus, inclusion of 20 patients per group was deemed sufficient.

Statistical analysis was performed using IBM SPSS Statistics 20.0 for Windows (IBM Corp, Armonk, NY). Enumerated data including gender, ASA physical status, reshivering rate, and nausea/vomiting incidence were compared using Fisher exact test or chi-square test, as appropriate. Comparison of continuous variables among the groups was performed using one-way analysis of variance with *post hoc* Bonferroni or Games-Howell tests; if the data are heterogeneity of variance, Kruskal-Wallis test was used. Paired-samples *t*-tests analyzed data within one group. Probability values <0.05 were considered to be indicative of statistically significant differences.

3. Results

From October 2012 to January 2013, of 153 gastrointestinal postoperative patients who were observed during the study period, 60 cases developed grades 2 and 3 shivering for more than 3 min with tympanic temperature <36°C that required treatment. The study groups were comparable with no significant difference in demographic profile, ASA physical status scores, duration of surgery, and basal temperature (Table 1).

Shivering stopped within 5 min in the pethidine and tramadol groups, and overwhelming majority (90%) stopped within 15 min in the AA group with two cases stopping within 20 and 25 min (Table 2). The shivering grade in AA group remained significantly elevated *versus* the pethidine and tramadol groups at 5 and 10 min ($P = 0.000$ in both comparisons). There were five cases of reshivering in the tramadol group; a significant increase *versus* the other two groups. The grades of reshivering were all level 1 and shivering lasted for only 1–4 min, no patient required intravenous pethidine rescue.

Tympanic temperature increased slowly but significantly within all patient groups during the 1-h postoperative observation period ($P < 0.01$ for all groups; Table 3). Temperature increased to a significantly greater extent in the AA group *versus* the pethidine and tramadol groups, beginning 10 min after treatment until the end of the observation period. There was no significant difference between tramadol and pethidine groups, at any observational time point.

Patient thermal comfort improved significantly within 5 min in the AA group and within 10 min in the other two

Table 1 – Patient characteristics.

Group	AA	Pethidine	Tramadol	*P*
Gender, male: female, *n*	12:8	7:13	8:12	0.243
Age, y	47.10 ± 9.9	45.70 ± 11.0	48.40 ± 9.8	0.709
Weight, kg	68.25 ± 6.86	65.95 ± 8.77	65.6 ± 7.42	0.503
ASA I:II	6:14	9:11	13:7	0.084
Preoperative tympanic temperature (°C)	36.84 ± 0.18	36.92 ± 0.12	36.91 ± 0.14	0.188
Surgery time, h	2.37 ± 0.27	2.38 ± 0.34	2.59 ± 0.44	0.096

Data are expressed as mean ± standard deviation, unless otherwise indicated.

Table 2 – Change in shivering grade during the 1-h observation period after drug administration.

Shivering grade	Grade 0	Grade 1	Grade 2	Grade 3
0 min				
AA	0	0	14 (70%)	6 (30%)
Pethidine	0	0	15 (75%)	5 (25%)
Tramadol	0	0	17 (85%)	3 (15%)
5 min				
AA*,†,‡	0	11 (55%)	7 (35%)	2 (10%)
Pethidine*	20 (100%)	0	0	0
Tramadol*	20 (100%)	0	0	0
10 min				
AA*,†,‡	5 (25%)	13 (75%)	1 (5%)	1 (5%)
Pethidine*	20 (100%)	0	0	0
Tramadol*	20 (100%)	0	0	0
15 min				
AA*	18 (90%)	1 (5%)	1 (5%)	0
Pethidine*	20 (100%)	0	0	0
Tramadol*	20 (100%)	0	0	0
20 min				
AA*	19 (95%)	1 (5%)	0	0
Pethidine*	20 (100%)	0	0	0
Tramadol*	19 (95%)	1 (5%)	0	0
25 min				
AA*	20 (100%)	0	0	0
Pethidine*	20 (100%)	0	0	0
Tramadol*	18 (90%)	2 (10%)	0	0
30–50 min				
AA*	20 (100%)	0	0	0
Pethidine*	20 (100%)	0	0	0
Tramadol*	20 (100%)	0	0	0
55 min				
AA*	20 (100%)	0	0	0
Pethidine*	20 (100%)	0	0	0
Tramadol*	18 (90%)	2 (10%)	0	0
60 min				
AA*	20 (100%)	0	0	0
Pethidine*	20 (100%)	0	0	0
Tramadol*	20 (100%)	0	0	0

*$P < 0.05$, intragroup comparison with 0 min.
†$P < 0.05$, AA group *versus* pethidine group.
‡$P < 0.05$, AA group *versus* tramadol group by the chi-square test.

groups. Thermal comfort values were significantly higher in the AA group than in the other two groups beginning at 5 min after drug treatment onset. In addition, reported thermal comfort levels were significantly higher in the tramadol group than in pethidine group beginning at 35 min after drug administration ($P < 0.01$). In the AA group, the thermal comfort index reached 50 mm or perceived thermoneutrality, at the end of the 1-h observation period, which was not achieved in the two other groups (Table 4).

There was no significant difference in blood lactic acid concentration among the three groups between arrival at the PACU and through 1 h after onset of drug administration. Lactic acid levels significantly and similarly decreased to close to the normal range in all three groups after treatment (Table 5).

Administration of AAs at postoperative shivering onset significantly increased blood glucose levels from 122.94 ± 6.12 mg/dL (6.83 ± 0.34 mmol/L) to 135.18 ± 9.18 mg/dL (7.51 ± 0.51 mmol/L), which was significantly higher than

Table 3 – Changes in tympanic temperature (°C) during the 1-h observation period after drug administration.

Group	AA	Pethidine	Tramadol
0 min	35.49 ± 0.15	35.50 ± 0.17	35.52 ± 0.15
5 min	35.71 ± 0.19*	35.70 ± 0.21*	35.72 ± 0.29*
10 min	36.00 ± 0.22*,†,‡	35.75 ± 0.15*	35.80 ± 0.14*
15 min	36.25 ± 0.18*,†,‡	35.81 ± 0.14*	35.88 ± 0.15*
20 min	36.37 ± 0.14*,†,‡	35.90 ± 0.13*	35.95 ± 0.15*
25 min	36.45 ± 0.11*,†,‡	35.97 ± 0.13*	36.02 ± 0.13*
30 min	36.55 ± 0.98*,†,‡	36.03 ± 0.12*	36.07 ± 0.12*
35 min	36.61 ± 0.11*,†,‡	36.10 ± 0.11*	36.15 ± 0.17*
40 min	36.70 ± 0.26*,†,‡	36.16 ± 0.10*	36.20 ± 0.27*
45 min	36.79 ± 0.12*,†,‡	36.19 ± 0.15*	36.23 ± 0.13*
50 min	36.85 ± 0.15*,†,‡	36.21 ± 0.11*	36.25 ± 0.13*
55 min	36.87 ± 0.15*,†,‡	36.28 ± 0.14*	36.32 ± 0.11*
60 min	36.89 ± 0.13*,†,‡	36.32 ± 0.12*	36.37 ± 0.11*

Data are expressed as mean ± standard deviation.
*$P < 0.05$, intragroup comparison *versus* time 0 min.
†$P < 0.05$, AA group *versus* pethidine group.
‡$P < 0.05$, AA group *versus* tramadol group.

glucose levels measured in the pethidine and tramadol groups ($P = 0.000$ in both groups; Table 5).

There were four, three, and four cases in the AA, pethidine, and tramadol groups, respectively, who asked to press the button of the pump administering patient-controlled epidural analgesia, and no difference among the groups ($P = 0.580$). The pain VAS did not differ among drug treatment groups for postoperative shivering between patient entry to the PACU and 1-h posttreatment onset (Table 5).

There were no cases of nausea and/or vomiting in the AA group; however, there were seven cases of nausea and three cases of vomiting in the pethidine group, and 11 cases of nausea and five cases of vomiting in the tramadol group (Table 6).

4. Discussion

This is the first prospective, randomized study showing that AA infusion can stop shivering and improve hypothermia and thermal comfort in the PACU. Infusion of AAs was begun after postoperative shivering induced by hypothermia was observed. This treatment reduced shivering severity within 5 min after infusion onset and overwhelming majority (90%) stopped shivering within 15 min after administration. Furthermore, AA infusion produced the most rapid improvement of hypothermia within 10 min after infusion onset and resulted in the greatest improvement in patient-reported thermal comfort 5 min after infusion onset *versus* pethidine and tramadol. In addition, the tramadol group had five cases of reshivering, whereas no reshivering episodes occurred in the AA and pethidine groups. Although the time until complete shivering cessation was significantly longer in the AA group than in the pethidine and tramadol groups, we observed that tympanic temperature increased most rapidly in the AA group, indicating enhanced thermogenesis. Thus, we conclude that AA infusion can effectively treat postoperative shivering and reverses hypothermia and improves thermal comfort more effectively than tramadol and pethidine.

Table 4 – Changes in thermal comfort during the 1-h period after drug administration.

Group	AA	Pethidine	Tramadol
0 min	30.50 ± 3.03	31.15 ± 2.83	30.55 ± 2.37
5 min	36.05 ± 3.02*,†,‡	32.60 ± 2.48	32.80 ± 2.33
10 min	40.25 ± 3.39*,†,‡	33.85 ± 2.18*	34.60 ± 2.21*
15 min	43.00 ± 3.80*,†,‡	34.65 ± 2.16*	35.75 ± 2.27*
20 min	44.85 ± 3.62*,†,‡	35.35 ± 1.84*	36.85 ± 2.46*
25 min	46.20 ± 3.09*,†,‡	36.30 ± 1.81*	38.10 ± 2.61*
30 min	47.35 ± 2.70*,†,‡	37.25 ± 1.80*	39.20 ± 2.95*
35 min	47.95 ± 2.24*,†,‡	37.95 ± 1.70*,§	40.20 ± 2.69*
40 min	48.50 ± 1.85*,†,‡	38.45 ± 1.73*,§	40.90 ± 2.73*
45 min	49.45 ± 1.73*,†,‡	39.20 ± 1.67*,§	41.85 ± 2.68*
50 min	49.70 ± 1.49*,†,‡	39.65 ± 1.69*,§	42.75 ± 2.59*
55 min	49.80 ± 1.32*,†,‡	40.10 ± 1.55*,§	43.65 ± 2.39*
60 min	50.00 ± 1.41*,†,‡	40.60 ± 1.43*,§	44.05 ± 2.11*

Data are expressed as mean ± standard deviation of the thermal comfort VAS scores.
*$P < 0.05$, intragroup comparison *versus* time 0 min.
†$P < 0.05$, AA group *versus* pethidine group.
‡$P < 0.05$, AA group *versus* tramadol group.
§$P < 0.05$, pethidine group *versus* tramadol group.

Along with nausea and vomiting, postoperative shivering and cold sensation are the leading causes of distress to patients in the early recovery phase following general anesthesia [2,17]. Besides shivering, perioperative hypothermia evokes thermal discomfort and morbid cardiac complications, triples the clinical incidence of surgical wound infections by directly impairing immune function, decreases cutaneous blood flow, which reduces tissue oxygenation, and substantially delays postoperative recovery from anesthesia, and increases hospitalization duration [17]. Postoperative thermal discomfort *per se* is not life-threatening; nonetheless, many patients recall feeling cold as the worst aspect of their surgery [18]. Therefore, perioperative hypothermia should be appropriately restored to normothermia as soon as possible. It is also well known that typical pharmacologic interventions for

Table 5 – Changes in blood lactic acid concentration (mmoL/L), glucose concentration (mg/dL), and pain VAS (cm, 0–10) after drug treatment.

Time	0 min	1 h After treatment
Lactic acid concentration (mmol/L)		
AA	1.89 ± 1.09	1.56 ± 0.70*
Pethidine	1.89 ± 0.22	1.73 ± 0.21*
Tramadol	1.77 ± 0.45	1.60 ± 0.43*
Glucose concentration (mg/dL)		
AA	122.94 ± 6.12	135.18 ± 9.18*,†,‡
Pethidine	123.66 ± 6.66	124.20 ± 7.56
Tramadol	122.94 ± 4.68	124.74 ± 4.86
Pain VAS (cm, 0–10)		
AA	1.95 ± 0.60	2.10 ± 0.31
Pethidine	1.90 ± 0.55	1.95 ± 0.39
Tramadol	2.00 ± 0.56	1.98 ± 0.39

Data are expressed as mean ± standard deviation.
*$P < 0.05$, intragroup comparison.
†$P < 0.05$, AA *versus* pethidine group.
‡$P < 0.05$, AA *versus* tramadol group.

Table 6 – Nausea/vomiting incidence.

Group	AA	Pethidine	Tramadol
Nausea	0/20*,†	7/20	11/20
Vomiting	0/20†	3/20	5/20

*$P < 0.05$, AA *versus* pethidine group.
†$P < 0.05$, AA *versus* tramadol group.

postoperative shivering does not raise body temperature but instead decreases shivering by resetting the shivering threshold to a lower level [2]. Therefore, Crowley and Buggy [19] suggested that "when we apply mechanisms to reduce shivering, we must ensure that we are adequately monitoring patient temperature and supplying adequate heat to patients."

By virtue of this fact, more attention should be paid to stimulating the body's own heat generation instead of solely inhibiting shivering. Nutrient-induced thermogenesis signifies the concept that all infused nutrients raise the body's energy expenditure and greatest thermic effect is ascribed to AAs and proteins, 30%–40% in the awake state [20].

It is well established that AA infusion before and/or during anesthesia and surgery protects from hypothermia and shivering [21]. However, the mechanism explaining AA-improved postoperative hypothermia might be different from mechanisms at work before or during surgery. The shivering threshold is usually 1°C below the vasoconstriction threshold [22]. Thus, shivering is a "last resort" defense that is activated only when maximal arteriovenous shunting and vasoconstriction are insufficient to maintain sufficient core temperature [18]. Nevertheless, the net efficiency of shivering thermogenesis is somewhat lower than that might be expected because muscle metabolism increases blood flow to peripheral tissues and, consequently, increases heat loss to the environment [2,18]. Haman [23] indicated that the adenosine triphosphate required to sustain involuntary muscle contractions during shivering is supplied through the oxidization carbohydrates, lipids, and proteins. These substrates are provided to shivering muscles at appropriate times and rates from intramuscular reserves and/or from other tissues via circulation [23]. Consequently, our study using "endogenous thermogenesis" from enhanced oxidative metabolism of AA infusion to stop shivering might partly attribute to their providing substrates for muscle during shivering, which can be proved by the fact that the thermogenic effect of intraoperative AA infusion in patients without shivering can only appear at about 2 h later [8]. Previous research [24] demonstrated that peripheral and core temperature contributed linearly to shivering control and that peripheral temperature was thought to influence approximately 20% of the shivering response. A conceivable mechanism by which AA infusion inhibits postoperative shivering is that average skin temperature can be raised by at least 4°C, which may be as effective as a 1°C core temperature increase in alleviating hypothermia [17]. In this case, the peripheral tissue temperature should have provided a sufficient temperature gradient to facilitate heat flow from the periphery to the core of the body [17]. As we presumed, shivering cessation due to AA infusion is likely unrelated to thermoreceptor resetting to a lower threshold but

instead is probably due to a direct thermogenic modulation of body temperature. In this study, we had not measured postoperative peripheral temperature; therefore, we cannot quantify AA infusion effects on peripheral temperature, which would be interesting to examine in future studies.

Thermal comfort is a subjective assessment of the thermal environment, which relies on the cortical integration of thermoafferent information arising from peripheral and central thermal inputs [22]. A given thermal stimulus can be perceived as either pleasant or unpleasant, depending on the core temperature [22]. The AA infusion increased core temperature was markedly higher than those obtained with pethidine or tramadol. In addition, increasing the skin temperature significantly can also improve thermal comfort [17]. So, as mentioned above, it is possible that AA infusion could have raised the skin temperature as well as the core temperature.

In this study, blood glucose concentration increased from 122.94 ± 6.12 mg/dL (6.83 ± 0.34 mmol/L) to 135.18 ± 9.18 mg/dL (7.51 ± 0.51 mmol/L) after continuous AA infusion for 1 h. This increase could be explained by AAs acting as substrates for the gluconeogenic pathway, which would temporarily increase endogenous glucose generation. Moreover, the endocrine milieu in postoperative patients is characterized by increased plasma concentrations of cortisol, adrenaline, and noradrenaline [25]. However, blood glucose values in the pethidine and tramadol groups were not altered by drug administration. In previous studies by our team, intraoperative AA infusion in patients undergoing gastrointestinal surgery also increased blood glucose concentration [8]. Blood glucose concentrations of 108–180 mg/dL (6–10 mmol/L) are clinically acceptable, both intraoperatively and shortly postoperatively; thus, the observed glucose elevation that occurred in the AA group in this study was irrelevant.

Surgical trauma elevates blood lactate levels [26]. Shivering is important in various metabolic derangements such as lactic acidosis [1], wherein blood lactate levels deviate from the normal range of 1–1.5 mmol/L. High blood lactate levels can hamper smooth recovery from anesthesia. We compared the baseline blood lactate levels of the three groups and again at the 1 h study end point. Posttreatment lactate levels were significantly lower than the pretreatment levels in all groups and remained close to the normal range. Thus, AA infusion had no significant effect on blood lactate levels.

Regarding side effects of the three drug regimens, tramadol and pethidine administration produced more nausea and vomiting, suggesting that these effects may be mediated by activation of μ-opioid receptors [6]. In our study, the nausea incidence in the pethidine and tramadol groups was higher than previously reported [13]. This might reflect that gastrointestinal surgery is a significant independent risk factor for postoperative nausea [27]. Conversely, no patients in the AA group suffered from nausea and/or vomiting. This is not surprising, given the propensity of opiates such as pethidine and tramadol to induce nausea.

Although there was no statistical difference in tympanic temperature between the tramadol and pethidine groups, tramadol measurements were slightly higher than the pethidine group. Moreover, some of the thermal comfort scales in the tramadol group were significantly higher *versus* the pethidine group. That may be due to tramadol inhibiting neuronal reuptake of norepinephrine and 5-hydroxytrypamine while facilitating 5-hydroxytrypamine release μ-opioid receptor activation, all of which likely influence thermoregulatory control. Tramadol reportedly has only slight thermoregulatory effects [6], whereas pethidine decreases metabolic heat production [28]. Unlike tramadol, pethidine inhibits the shivering threshold twice as much as the vasoconstriction threshold [5]. This special antishivering effect of pethidine is primarily mediated by disproportionate reduction in the shivering [5].

In conclusion, AA (Novamin) infusion is a new method to treat postoperative shivering, alleviates hypothermia, and improves thermal comfort more effectively than tramadol and pethidine with less nausea and vomiting and causes a clinically acceptable blood glucose increase with no shivering recurrence in the PACU setting. In other words, Novamin infusion is a method to cure postoperative shivering with hypothermia.

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Appendix

Composition of Novamin 18AA-II (per 1000 mL)

L-Alanine	16.3 g
L-Arginine	11.2 g
L-Aspartic acid	3.3 g
L-Cystine	0.2 g
L-Glutamic acid	5.7 g
Glycine	7.9 g
L-Histidine	6.8 g
L-Isoleucine	5.7 g
L-Leucine	7.9 g
L-Lysine acetate	12.7 g
L-Methionine	5.7 g
L-Phenylalanine	7.9 g
L-Proline	6.8 g
L-Serine	4.5 g
L-Threonine	5.7 g
L-Tryptophan	1.9 g
L-Tyrosine	0.3 g
L-Valine	7.3 g
Sodium metabisulfite	0.3 g
Glacial acetic acid	approximately 2.75 mL
Diluted with water for injection to	1000 mL
AA	114 g
Nitrogen	18 g
Total energy	460 kcal
pH	approximately 5.6
Osmotic pressure	approximately 1130 mOsm/kg·H_2O