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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%.