Open Journal of Anesthesiology, 2017, 7, 287-295
http://www.scirp.org/journal/ojanes
ISSN Online: 2164-5558
ISSN Print: 2164-5531

Amino Acids during Perioperative Period

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How to cite this paper: Yokoyama, T., Yamaoka, I., Hitosugi, T. and Selldén, E. (2017) Amino Acids during Perioperative Period. *Open Journal of Anesthesiology*, **7**, 287-295.
https://doi.org/10.4236/ojanes.2017.79029

Received: August 8, 2017
Accepted: September 18, 2017
Published: September 22, 2017

Abstract

During anesthesia, thermoregulation is impaired and hypothermia will frequently occur in most patients. Hypothermia affects immunologic activity, bleeding tendency and the recovery from anesthesia. Therefore, it may prolong hospital stay, and increase morbidity, e.g. surgical site infections, cardiac events and multiple organ dysfunctions in trauma. External warming is often used to prevent hypothermia. However, infusion of amino acids is also valuable to prevent hypothermia due to their enhanced thermogenic action under anesthesia. During surgery, amino acids administration would maintain the body homeostasis, and counteract the disadvantageous fasting metabolism. Postoperatively, amino acids may be advantageous for the healing of the surgical wound. Thus, appropriate nutritional management, including glucose, during the perioperative period would prevent catabolism, frequently occurring after surgery. Protocols like ERAS (Enhanced Recovery After Surgery) are proposed for quick recovery after surgery. ERAS protocol recommends preoperative carbohydrate and early enteral nutrition, but does not include infusion of amino acids during the perioperative period. During prolonged surgery, patients clearly need good nutritional support. In this article, we intend to describe the problems of hypothermia briefly, and explain the mechanism of amino acids in hypothermia prevention. In addition, we address some evidences of nutritional management during the perioperative period.

Keywords

Anesthesia, Hypothermia, Amino Acids, Nutrition

1. Introduction

During the perioperative period, hypothermia initiates adverse events, which could lead to poor outcome after surgery [1] [2] [3]. Administration of amino acids during the perioperative period has been demonstrated to prevent hypothermia during anesthesia [4]. In addition, amino acids may be important to optimize perioperative nutritional management. In this point, amino acids may be related to the enhanced recovery.

2. Hypothermia during Surgery

Core temperature is maintained at around 37 degree centigrade, via a delicate and thoroughly controlled system, including both central and peripheral components [5]. However, sympathetic nerve function is usually suppressed during general anesthesia and even, to some extent, during spinal anesthesia [6] [7].

Hypothermia during anesthesia is caused by decreased heat production as well as increased heat loss and impaired hypothalamic thermoregulation [8]. Body heat redistribution between core and peripheral tissues would also contribute. Specifically, inadvertent hypothermia consists of 3 phases [9] [10]. Finally, temperature may reach to a stagnant phase at low degree. Room temperature, evaporation from the surgical field, and cold infusion would have additive effect on hypothermia. Specific heat capacity of human body is 0.83 kcal/kg, and specific heat capacity of infusion solution and blood transfusion preparation is around 1.0 kcal/kg [11]. 50 kcal of heat loss, which correspond to around 4 litre of infusion at 25 degree centigrade, decreases body temperature by around 1 degree centigrade.

3. Problems and Benefits of Hypothermia

Hypothermia often causes shivering after anesthesia, which may increase oxygen consumption 3 to 4 times, and increases the risk of ventricular tachycardia and morbid cardiac events [1]. There is a report that body cooling might cause decreased oxygen pressure in the brain tissue when shivering started [12]. Hypothermia prolongs recovery from anesthesia due to decrease in minimum alveolar concentration of inhalation anesthetics, and due to prolonged recovery of muscle relaxants [13].

Hypothermia reduces platelet function and impairs enzymatic reaction of the coagulation cascade, which increases blood loss during surgery and the risk of transfusion [14] [15] [16].

Hypothermia would promote surgical infection and delay wound healing, most likely due to decreased subcutaneous oxygen tension [17], and impaired immune function. Warming patients before surgery reduces the risk of surgical infection [18]. Hypothermia may be associated with increased morbidity and mortality after major surgery [19].

On the other hand, hypothermia may be protective in the brain tissue during oxygen deficiency [20], since brain metabolism and thus oxygen consumption decreases along with the temperature. Metabolic rate in the brain decreases by 6 to 7% by every 1 degree centigrade decrease in the body temperature [21]. Besides, hypothermia had an additive effect with barbiturate for brain protection [22].

4. Prevention of Hypothermia

Active warming systems, for example forced-air warming blowers and infusion fluid warming devices, are frequently used to prevent hypothermia in the operation room. In the case of forced-air warming blower, however, a risk of low temperature burn injury is reported [23]. In addition, it is questioned whether it may increase the risk of bacterial pollution of the surgical field [24]. When a large volume of infusion is required, infusion fluid warming devices are useful. However, they might be less effective at low infusion speed.

Mizobe *et al.* reported that fructose infusion is useful for avoiding hypothermia [25]. It requires 2.0 g/kg of fructose for 4 hours. However, it has been pointed out for a long time that equivalent dose of fructose infusion may decrease ATP in the liver possibly leading to hepatic damage [26]. In addition, fructose infusion would cause acidosis and hyperuricemia. Fructose infusion, therefore, should be avoided during perioperative period.

Selldén, one of authors of this article, reported that infusion of amino acids before or during general anesthesia is useful to prevent hypothermia [27]. In addition, amino acids infusion was demonstrated to shorten hospital stay [2]. Kasai reported that infusion of amino acids is useful to prevent hypothermia not only during general anesthesia but also during spinal anesthesia [6] [7]. Osmotic pressure of amino acids solution is very high, and rapid infusion may cause phlebitis and imbalance of serum electrolytes. Clinically, however, slow infusion, around 240 kJ/h, preferably in a central venous line, for a few hours usually cause no problems. This method is convenient and has additive effect with other warming systems.

5. Metabolism of Amino Acids

The methodology using amino acids is simple in that it stimulates internal heat production in the body, compared to heating techniques heavily depending on medical devices. The metabolic fate of the infused amino acids falls roughly into two categories: oxidation for energy production and/or building blocks for protein synthesis. Irrespective of pathway, large amounts of energy are required for amino acid metabolism, and eventually heat production. About twenty percentages of caloric contents in amino acids are consumed throughout the metabolic pathway, which differs from those of glucose and fatty acids (0% - 5%) [28]. In agreement with such differences among macronutrients in energy consumption through metabolic pathways, attenuation of hypothermia by intravenous infusion of amino acids mixture, but not by glucose and lipid, is also effective in an anesthetized rodent model.

6. Mechanism for Preventing Hypothermia

Similar with conscious rats, intravenous amino acids infusion clearly elevates protein synthetic rates in skeletal muscle accounting for a major proportion of the body protein synthesis [29]. These findings imply a subsequent production of heat due to greater energy consumption in skeletal muscle. The increase of muscular protein synthesis in anesthetized rats given amino acids is characterized by a marked elevation in plasma insulin concentrations. Most probably, this initiates phosphorylation of several translation initiation factors. Those factors are required for the stimulation of protein synthesis, through protein kinase B and mammalian target of rapamycin [30]. The elevated plasma insulin levels under anesthetized state are features common to an animal model and human beings. Intriguingly, not only phosphorylation of these signaling transduction components and translation initiation factors but also amino acid-stimulated increase in oxygen consumption and core temperature is clearly cancelled by inhibiting the amino acid-induced elevation of plasma insulin by a pancreatic hormone inhibitor, somatostatin [31]. In terms of amino acids oxidation, intravenous infusion of amino acid boosts degradation of myofibrillarprotein [32]. This phenomenon could be the result of increased muscle protein turnover due to rapid infusion of amino acids. In that case both degradation and anabolism should be approximately equal. Interestingly, core temperature of anesthetized and conscious rats well correlates with plasma 3-methylhistidine, a marker of myofibrillar protein breakdown [32]. It is described that glucose infusion clearly inhibits degradation of myofibrillar protein through down-regulation of ubiquitin proteasome genes expression in rats [33]. However, it is still not clear how amino acids regulate the system and hence promote the myofibrillar protein degradation. The elevation in both synthesis and degradation rate of amino acids in the skeletal muscle provide collateral evidence of the critical role of elevated turnover in muscular protein metabolism, well known to generate heat. During anesthesia, when thermoregulation is impaired and the central inhibitory pathway in metabolism is depressed, the heat production in this process is increased compared to the awake state [4]. Another finding suggesting a key role of skeletal muscle as an organ for thermogenesis, was that infusion of amino acid mixture showed no effect on hypothermia in a rat model of skeletal muscle atrophy [34]. Moreover, in patients, splanchnic tissues did not change their proportion of the metabolism during amino acid infusion in the anesthesia and surgery period, whereas the extra-splanchnic metabolism was markedly enhanced [35]. In this aspect, skeletal muscles are able to accommodate a large protein turnover. Studies in patients with cervical spine ruptures and muscular atrophy showed increase postprandial plasma insulin levels [36]. Furthermore, intravenous infusion of amino acid mixture significantly elevates the thermoregulatory threshold for cold-defensive responses such as vascular contraction and shivering in both anesthetized and conscious human subjects [37]. All these findings intrigue linkage responses between central nervous system and muscular protein metabolism. Accumulation of heat in the body by infusion of amino acids, the most efficient macronutrient for protein synthesis, signifies the increase in both the order of biological molecules and disorder causing heat generation. We postulate the mechanisms of heat accumulation by amino acids (**Figure 1**).

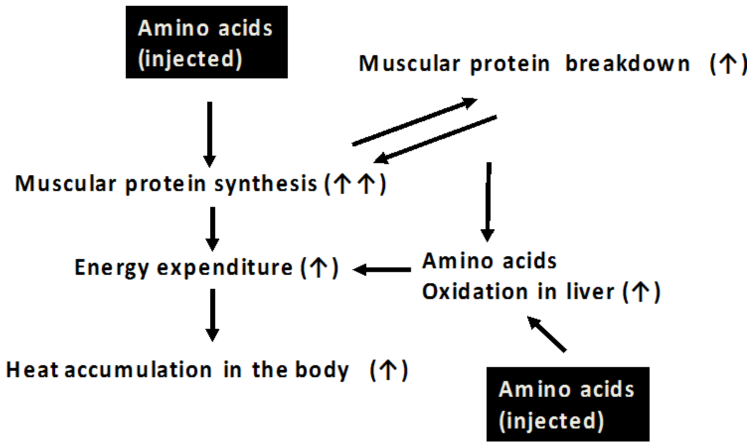

Figure 1. Amino acids infused in the body stimulate both protein synthesis and breakdown in the skeletal muscle and oxidation of amino acids in the liver, resulting in further increases in not only oxidation of amino acids in liver but also provision of building blocks for protein synthesis. All reactions require larger amounts of energy compared to glucose or lipid metabolism, leading to accumulate heat in the body.

7. Nutritional Management during Perioperative Period

Anesthesiologists have increased interest in nutritional management during perioperative period, however it is difficult to evaluate. It is well established that glucose is necessary for biological activity even during general anesthesia. The central nervous system, red blood cells and kidney medulla require only glucose as energy source. The brain consumes around 120 g of glucose a day for around 70 kg of patients, and 200 g of glucose is required except muscle exercise. Glucose is stored as glycogen in the body, but the total amount of glycogen is not sufficient for basal metabolism for one day. Shortage of glucose induces gluconeogenesis mainly in the liver [38]. Around 90% of gluconeogenesis uses amino acids as raw materials, and glycerol is used for the remaining around 10% of gluconeogenesis. There are various glucogenic amino acids, of which, after deamination, carbon structure is utilized for gluconeogenesis via pyruvate or oxaloacetate. Fatty acids are oxidated in mitochondria in the liver. Acceleration of ketogenesis in the liver causes ketonemia, which indicates shortage of glucose [39]. On the other hand, too much glucose is utilized for steatogenesis.

Yokoyama, one of authors of this article, reported that anesthetic management during surgery without glucose increases serum ketone bodies [40]. In patients undergoing orthopedic surgery, ketonemia is observed in a few hours from the start of surgery, but it was effectively avoided by 1.0% glucose infusion. Yamasaki *et al.* also reported similar results in patients undergoing head and neck surgery [41]. In addition, Mikura *et al* reported that infusion without glucose enhanced muscle protein breakdown in rat model [33]. Administration of amino acids and glucose in combination could be expected to contribute in nutritional management during the perioperative period. However, recently, a preliminary study has reported that combination of glucose and amino acid administration may offset the effect of amino acids in hypothermia prevention during anesthesia and surgery [42]. These results suggest that muscle protein breakdown might be required, along with protein synthesis, to attenuate hypothermia. It might be supposed that glucose and amino acids are not compatible with each other.

We reported that enteral administration of amino acids is also useful for preventing hypothermia in an animal model [43]. Oral administration is therefore also effective, but it may increase the risk of nausea and vomiting, since some amino acids may decrease stomach-emptying rate, most probably to avoid quick changes in serum nutrients. In addition, we found that orally administrated amino acids were badly tolerated due to bitter taste. Therefore, it is not possible to use this convenient way of amino acid intake preoperatively.

8. Conclusion

In conclusion, intravenous infusion of amino acids provides a useful and simple method for preventing hypothermia during anesthesia, by internal heat generation in the body, and it is well tolerated by the patients. However, we have to consider the principles of nutritional management for enhanced recovery. Further studies are required in this field. For administration of amino acids, ample room has been left for improving the administration timing, dose and route. In future, amino acids should be utilized not only to maintain body temperature but also to provide nutritional balance during perioperative period.

Author Contributions

Yokoyama T., Yamaoka Iand Hitosugi T. wrote the paper; Selldén E. supervised the manuscript.

Supported by Conflict-of-Interest Statement

Authors declare no conflict of interests for this article.

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