# *Role of Amino Acids Infusion in Prevention of Anesthesia Induced Hypothermia and Postoperative Shivering*

**THESIS**

Submitted for partial fulfillment of the M.D. degree in anesthesiology

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2007

# Acknowledgement

All gratitude is due solely to Allah.

No word can fulfill the feeling of gratitude and respect I carry to ***Prof. Dr. Medhat Mohamed Younes***, Professor of Anesthesiology and Intensive Care, Ain Shams University, for all his efforts without which, this work can't be achieved. I am thankful for his support, constructive guidance and real interest in the progress of this work.

It gives me a great pleasure to express my sincere gratitude to **Prof. Dr. Azza Mohamed Shafiek Abdel Maged,** Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for her valuable supervision and eminent guidance spending quite precious time for the proper achievement of this work..

I would like to express my deepest appreciation to **Dr. Fahmy Saad Latif**, Assistant Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for his helpful supervision and continuous encouragement. It is really a great honor to work under his guidance and supervision.

I should also express my sincere appreciation to **Dr. *Mohamed Anwar Elshafei***, Assistant Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for his

kind advice, continuous encouragement, valuable suggestions and his great effort throughout the whole work.

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# Conclusion and Recommendations

In conclusion, this study showed that amino acid infusion before and/or during general anesthesia and surgery restored core body temperature at awakening and almost eliminated postoperative shivering and the related adverse effects without uncompensated extra- hemodynamic or metabolic loads.

The effects of a relatively harmless amino acid infusion *(strictly limited to those who can cope with the possible side effects of amino acid load)* on complex mechanisms of temperature balance are dramatic and they are likely to enhance the quality of patient care.

It is recommended to start the amino acid infusion one hour before the induction of anesthesia for operations lasting between two to four hours and in general, the onset of amino acids infusion has to be tailored according to the expected duration of surgery keeping in mind delayed thermogenic effect of amino acid infusion.

# Aim of the Work

This present study is designed to evaluate the ability of amino acids infusion to prevent anesthesia induced hypothermia and postoperative shivering in patients receiving general anesthesia for abdominal surgeries.

# Discussion

During general anesthesia, there is a marked decrease in energy expenditure heat generation. In addition, central thermoregulatory function is impaired, delaying hypothermia defense mechanisms. The hypothermic effect is compounded during prolonged operations especially those in which thoracic and abdominal cavities are exposed to operating room temperatures. Postoperatively, hypothermic patients are uncomfortable and at risk of developing several hypothermia–related complications, such as shivering, coagulation disturbances, ischemic cardiac events and decreased resistance to wound infections which is known to prolong hospitalization. Consequently, the prevention of intra-operative hypothermia is of interest ***(Sellden and Lindahl, 1999).***

Many warming devices are in use to prevent heat loss, but little attention has been paid to stimulate the body's own heat generation. All nutrients raise energy expenditure, and the highest thermic effect is ascribed to amino acids and proteins, 30-40 % in the awake state ***(Sellden, 2002).***

Moreover, approximately 60 % of the extra heat produced in response to amino acid administration accumulates, thus increasing the temperature of mixed venous blood. The thermic effect of amino acids is augmented during general anesthesia, and preoperative amino acids infusion thereby prevents the anesthesia – induced reduction in metabolism and the accompanying postoperative hypothermia ***(Sellden et al., 1996a).***

During anesthesia, central thermosensors are silenced and hence, amino acid thermogenesis is exaggerated. The amino acid-induced heat generation during anesthesia predominantly occurs in extra-splanchnic tissues, most probably in skeletal muscle. It may reflect an increased protein turnover, as both protein breakdown and synthesis are energy-consuming processes known to generate heat. Possibly,

amino acid infusion provides substrates, otherwise mobilized from the body's own tissues, needed for wound healing and immunological function. However, other cellular mechanisms may also contribute to this non-shivering thermogenesis ***(Sellden, 2002).***

At awakening from anesthesia, post-operative hypothermia may be prevented without shivering. The tissues involved and the mechanisms by which nutrients stimulate heat production are still not completely understood. However, these findings support the existence of an inhibitory action normally exerted by central thermosensors, in order to maintain oxidative metabolism within certain limits, to prevent hyperthermia ***(Sellden, 2002).***

Amino acids infusion not only increases the metabolic rate and the resting core temperature but also increases the set point for all thermoregulatory autonomic responses. ***(Nakajima et al., 2004)***

It was found that, preoperative infusion of amino acids effectively prevents spinal anesthesia induced hypothermia by maintaining a higher metabolic rate and increasing the threshold core temperature for thermal vasoconstriction ***(Kasai et al., 2003).***

In the present study, the rectal temperature was increased after amino acids infusion by approximately 0.15$^{o}$C/h in group I and group II before onset of anesthesia. This is constant with the study conducted in 2004 by Nakajima et al. which showed that amino acids infusion for 150min in nine male volunteers had increased their resting core temperature by 0.3±0.1 (mean±SD). ***(Nakajima et al., 2004)***

Then, rectal temperature was following the usual pattern of general anesthesia – induced hypothermia, it was markedly decreased immediately after induction and during the first hour of anesthesia. This reduction was observed by the same rate in the three studied groups of the present study with simultaneous rapid reduction in the core – to – peripheral temperature gradient (from about 4.5$^{o}$C before induction of anesthesia to about 2$^{o}$C after one hour from its induction) suggesting that the amino acids infusion did not affect the *rate* of initial reduction of temperature due to redistribution of body heat after induction of anesthesia ***(Sellden et al., 1996b)***.

However, the rate of temperature reduction was progressively decreased after this first hour. Furthermore, the magnitude of this reduction was different in the three groups being less in the amino acids treated groups as indicated by the significant Groups–Time interaction.

This was most probably due to the increased metabolic rate enhanced by the infused amino acids. This increase compensates for the heat loss to the environment which distinguishes this period ***(Kasai et al., 2003).***

Postoperatively, the recovery from hypothermia was significantly faster in the amino acids treated groups than in the control group. Not only this, but also recovery from hypothermia was faster in the group I than group II indicating that infusion of amino acid started one hour before induction of anesthesia and continued for one hour intra-operatively was better than its infusion for two hours preoperatively as regard recovery from anesthesia – induced hypothermia in operations last from 2 to 4 hours. This may be attributed to the delayed thermogenic effect of amino acids that occurs 30-90 min after the end of amino acid infusion ***(Sellden, 2002).***

These findings are supported by many prospective randomized studies. In 1996, Sellden et al showed that preoperative infusion of amino acids in 16 female patents underwent hysterectomy and sex healthy women elevated significantly their mean rectal temperature by more than 0.2 $^{o}$C per hour before induction of anesthesia as compared with infusion of nutrient free saline in another 8 patients (the control group). After induction of anesthesia, they reported immediate temperature reductions in all patients by nearly the same degree however; during the entire period of anesthesia and surgery, the decrease in temperature was significantly greater in the control group than in the amino acid treated groups ***(Sellden et al., 1996b).***

The same results were obtained by Sellden and Lindahl in 1999, after they have studied 45 patients receiving amino acids before anesthesia and 30 control patents receiving acetated Ringer's solution. The intraoperative decline in core temperature was significantly more in control patients, 0.8 ± 0.1$^{o}$C/h (mean ± SD) with maximal decrease

of 1.2 ± 0.1 °C, than in amino acids treated patients, 0.5 ± 0.1 °C/h, with maximal decrease of 0.8 ± 0.1 °C ***(Sellden and Lindahl, 1999).***

In 2005, Chandrasekaran et al, conducted a pilot study on 10 patients underwent complex major colorectal operations who received amino acids infusion just after induction of anesthesia but prior to skin incision and 10 control patients who underwent similar surgical procedures. They found that the body temperature was statistically significantly reduced in both groups at skin incision when compared with temperature prior to induction of anesthesia. However, the increase in body temperature after this initial reduction till recovery period was statistically significant in the study group but not so in the control group ***(Chandrasekaran et al., 2005).***

Kamitani et al showed in 2006, that amino acids infusion started at induction of anesthesia in 42 patients (duration of surgery of 180 min or more) prevented intraoperative hypothermia, and their infusion in 32 patients (duration of surgery less than 180 min) decreased significantly the number of patients with tympanic temperature of less than 35.5°C as compared with saline infusion ***(Kamitani et al., 2006).***

180 patients underwent off-pump coronary artery bypass grafting were included in a study conducted by Umenai et al in 2006. The esophageal core temperature at the end of surgery was 35.6 (35.3–35.8)°C [mean (95% CI)] in the saline infused patients and 36.1 (35.9–36.3)°C in the amino acids infused patients ($p<0.05$) ***(Umenai et al., 2006).***

Comparable results were obtained from studying the effect of preoperative amino acids infusion on thermoregulatory response during regional anesthesia. In 2003, Kasai et al measured the core temperature 90 min after induction of spinal anesthesia in 35 patients. They found that the mean core temperature was significantly higher in the amino acids treated patients than in the saline infused patients, being 36.6 (0.1)°C and 35.8 (0.1)°C respectively [mean (standard error of the mean)] ***(Kasai et al., 2003).***

Rectal –to– skin temperature gradient was identical in the three groups even when the core temperature was higher in the amino acids treated groups during the plateau phase of anesthesia – induced hypothermia and during early postoperative period which indicates

that the threshold for thermoregulatory vasoconstriction was synchronously elevated in these groups ***(Nakajima et al., 2004)***.

This vasoconstriction was most probably responsible for the marked progressive increase in the rectal –to– skin temperature gradient that was observed after two hours from the onset of anesthesia then decreased gradually as the core temperature was approaching its resting value.

The mechanisms by which amino acid infusion increases the set point are not clear and remain unknown. However, peripherally infused amino acids are unlikely to cross the blood–brain barrier. It is therefore unlikely that amino acids *directly* alter central thermoregulatory control ***(Nakajima et al., 2004)***.

As regard hemodynamics, amino acids infusion was proved to have no significant effects on heart rate or mean arterial pressure when compared with infusion of the same amount of saline in awake, non-anesthetized volunteers ***(Nakajima et al., 2004).*** On the other hand, hypothermia and anesthesia itself have profound effects on hemodynamics.

As observed in the present study, many other researchers showed that there was no significant difference in heart rate between the studied groups during preoperative, intra-operative or postoperative periods ***(Sellden and Lindahl, 1998a).***

However, in some studies investigated the effect of hypothermia (did not include amino acids infusion), the heart rate was significantly reduced intra–operatively ***(Frank et al., 1995)*** or postoperatively ***(Chi et al., 2001)*** in the hypothermia–groups.

This controversy is most probably attributed to the big significant difference in the core temperature between the two studied groups (36.7±0.1 (mean ± SD) vs. 35.3±0.1ºC in Frank et al. study, and 36.9±0.3 vs. 34.2±0.2 ºC in Chi et al. study that yields differences of 1.4ºC and 2.7ºC respectively) compared with that of our study (35.9±0.22 vs. 35.15±46 ºC which makes a difference of 0.75ºC, 2-4 times smaller than those of the previous two studies). As the hypothermia–induced bradycardia is temperature dependent; it is not surprising that a significant difference in heart rate between the studied groups could not be detected in the current study.

Furthermore, the reduced heart rates in the previous studies, despite of being statistically significant, it was clinically insignificant as it was less than 10 beats/min at any given time. So, it was concluded that the changes in the mean heart rate observed in the current study were only attributed to the effect of surgery and anesthesia.

In a recent study conducted on 170 orthopedic surgical patients, the significantly increased heart rate observed on arrival to the post-anesthetic care unit (PACU) was in the shivering patients those forming about 25% of the studied patients ***(Kiekkas et al., 2005).***

A similar shivering percentage was observed in the present study in the control group (23.3%) that may be the cause of the larger variability in the heart rate observed postoperatively in this group compared with the other two groups as indicated by the standard deviation (16.9, 17.8 and 18.5 bpm for group I, group II and group III respectively)

As regard mean arterial blood pressure, it was proved that mild hypothermia produces hypertension due to the thermoregulatory vasoconstriction ***(Greif et al., 2003)***

During anesthesia, this vasoconstriction is developed only after two to three hours and strongly related to the level of serum norepinephrine ***(Frank et al., 1995).***

In the current study, there were considerable variations from baseline in blood pressure during the study period, but there were no significant differences between the three groups at any time throughout anesthesia and surgery although the magnitude of hypothermia was not the same in these groups. This is constant with the findings reported by Sellden et al in 1996 ***(Sellden et al., 1996b).***

In a more recent study, Sellden and Lindahl obtained the same results in 1998 by measuring the arterial blood pressure, heart rate and plasma adrenaline and noradrinaline levels in 14 patients scheduled for gall bladder surgery. They found that there were no significant differences between patients receiving amino acids infusion and those receiving nutrient-free saline as regard these measurements in spite of the considerable variations from the baseline ***(Sellden and Lindahl, 1998a)***.

The elevated threshold for thermoregulatory vasoconstriction response to hypothermia which was suggested to be achieved by amino acids infusion could be the explanation of these comparable blood pressure readings in the studied groups during anesthesia ***(Nakajima et al., 2004).***

In the postoperative period however, group III showed a significantly higher blood pressure compared with the other two groups. This difference may be attributed, in addition to hypothermia, to the postoperative annoying shivering observed in a higher rate in this group.

Although a study showed that there was no significant difference in blood pressure postoperatively between normothermic and mild hypothermic patients underwent cerebral aneurysm surgeries ***(Chi et al., 2001)***, yet a more recent study showed that a significantly higher blood pressure was recorded in hypothermic patients on arriving to PACU ***(Kiekkas et al., 2005).***

The time of measurement was different in these two studies, being immediately after extubation in the former study while it was after arriving to PACU in the later one. This is constant with our observation that the higher blood pressure was reported to be significant later in postoperative period then gradually decreased to be the same as in the other two groups within one hour.

Arterial oxygen saturation was unchanged during the study in all patients, being constantly 97 – 100%. This result could be explained by the fact that all patients were receiving high inspired oxygen saturation during the intra-operative period and early postoperative period (40%) which compensated for any expected increase in oxygen consumption due to increased metabolic rate (either due to amino acids infusion or shivering). Another explanation was reported by Sellden et al., in 1996, who suggested that an increase in ventilation was the cause of keeping normal comparable arterial oxygen saturation ***(Sellden et al., 1996b)***.

As regard $P_aCO_2$, the present study showed that infusion of amino acids in un-anesthetized patients was accompanied by slight, yet significant, increase in $P_aCO_2$ from the base line reading in the amino acids treated groups especially in group II than in group I (2.3 mmHg

and 1.3 mmHg respectively). However, this increase was within the normal range of $P_aCO_2$ (38.4 mmHg and 37.5 mmHg for group II and group I respectively). This was explained by the increased metabolic rate (oxygen uptake and energy expenditure) induced by amino acids infusion as proved by many earlier studies ***(Sellden et al., 1996b)***, ***(Sellden and Lindahl, 1998a) and (Sellden and Lindahl, 1999)***.

During intra-operative period, the end tidal $PCO_2$ was maintained to be 34-36 mmHg by readjustment of mechanical ventilation. That is why $P_aCO_2$ levels during this period were the same in the three groups especially at the end of procedures.

However, $P_aCO_2$ was significantly higher in the control group than in the amino acids treated groups during the postoperative period. This finding was most probably attributed to mild hypoventilation that might be occurred in some patients of this group due to shivering and pain in addition to the increased metabolism induced by shivering itself ***(Thomas et al., 2000).***

This hypoventilation was not sufficient to produce clinically significant hypercapnia as the mean level was below 40 mmHg (the maximum mean reading was 39.2 mmHg). Furthermore, this high normal $P_aCO_2$ was not constant in all patients of this group as indicated by wider standard deviation (5.6 mmHg) as compared with that of the baseline (2.6 mmHg).

It seems that the increased oxygen uptake and metabolic rate induced by amino acids infusion was compensated by increased ventilation to maintain within–normal $P_aCO_2$ ***(Sellden et al., 1996b).***

pH was comparable in the three studied groups throughout the study period. However, it showed slowly progressive decrease till it became significantly lower than its baseline value at the end of procedures. This difference, in spite of being statistically significant, was not clinically significant in about 75% of patients as indicated by inter – quartile range of 7.33 – 7.47 at its lowest value.

Then pH returned to its preoperative level shortly after recovery from anesthesia. This comparable, between–groups pH could be explained by the well established fact that tissue hypoxia, and thus metabolic acidosis, is unlikely to be developed by hypothermia per se because the decreased tissue oxygen availability produced by