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Administration of Intravenous Amino Acids Attenuates Postoperative Hypothermia in Patients Undergoing Percutaneous Nephrolithotomy

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Abstract

Objective: Amino acids attenuate hypothermia during the perioperative period by increasing thermogenesis and stimulating energy consumption. Percutaneous nephrolithotomy (PCNL) induces profound hypothermia owing to the use of large volumes of irrigating fluids. The role of amino acids in this group of surgeries for hypothermia and shivering prevention has been evaluated in this study because there is no available literature of concern.

Methods: This prospective randomised controlled trial was conducted in patients undergoing PCNL. Group A received amino acids at 60 mL h^{-1} an hour before surgery until the end of surgery. Group C received normal saline infusion. Perioperative nasopharyngeal temperature, haemodynamics, and postoperative shivering were recorded.

Results: Although there was no significant difference in temperature in the intraoperative period, postoperative decrease in the temperature was less in the amino acid group. In the postoperative period, 2 patients in the amino acid group and 11 patients in the control group experienced shivering.

Conclusion: Intravenous administration of amino acids attenuated postoperative hypothermia and reduced shivering in patients undergoing PCNL without any adverse effects.

Keywords: Amino acids, hypothermia, nephrolithotomy, percutaneous

Introduction

Hypothermia is a common occurrence in the perioperative period and can lead to complications, such as surgical site infections, major adverse cardiovascular events, and prolonged hospital stay.[1,2] Although inhibition of central thermoregulatory mechanisms is postulated as a cause for hypothermia, the decrease in basal metabolism, redistribution of heat from core to periphery and heat loss secondary to anaesthetic-induced vasodilatation are also contributory factors.[3] Methods aiming to prevent hypothermia, such as the use of forced air warming and fluid warmers, commonly target the reduction of heat loss.[4] Dependence on the area exposed for surgery and the cost of these devices are the limiting factors. However, administration of intravenous amino acids (AAs) in patients undergoing anaesthesia and surgery aims to attenuate hypothermia by stimulation of oxidative metabolism and heat production and is not dependent on other factors.[5] AAs not only elicit thermogenesis but also produce a synchronous increase in thermoregulatory defence thresholds.[6] AA infusion increases the heat produced by 5-fold under general anaesthesia compared with awake patients, leading to normothermic smooth emergence of patients without shivering per many studies.[7-11]

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Endoscopic-urologic procedures use large volumes of irrigating fluids, which can lead to perioperative hypothermia. Percutaneous nephrolithotomy (PCNL) for staghorn renal calculus is of particular concern as the amount of irrigation fluid used is significant and the duration of surgery may be prolonged, both of which contribute to temperature loss. This results in increased bleeding because of altered coagulation, delayed recovery, and shivering in the postoperative period. Hypothermia in this specific group of patients being treated with AAs has not been studied yet. Hence, this study was designed to evaluate the effect of intravenous AA infusion on hypothermia and postoperative shivering in patients undergoing PCNL.

Methods

This prospective randomised controlled trial was conducted in a tertiary care centre after approval from the institutional ethics committee (NIMS Institutional Ethics Committee, Hyderabad, India). The study was registered in the clinical trial registry of India (no. CTRI/2015/01/005532). Written informed consent was obtained from all the patients before participation in the study. A total of 32 patients with the American Society of Anesthesiologists physical status I and II who posted for elective PCNL under general anaesthesia were included in the study (Figure 1). Patients with a body mass index of >30 kg m^{-2}, altered renal parameters, and hepatic diseases and patients receiving medications likely to alter thermoregulation, such as acetaminophen and non-steroidal anti-inflammatory drugs, were excluded. After inclusion, patients were excluded if there was haemodynamic instability owing to bleeding or sepsis requiring infusion of fluids, blood, and inotropes intraoperatively. Patients were randomly assigned into 2 groups using computer-generated simple randomisation. Group A (n=16) received a mixture of 16 AAs; 10% Aminoven^{R} (with total nitrogen of 16.2 g L^{-1}, Fresenius Kabi, Austria) was given as an infusion at the rate of 60 mL h^{-1} corresponding to 100 KJ h^{-1}. Group C (n=16) received 0.9% saline at the rate of 60 mL h^{-1}. The infusion was started 1 hour before the induction of anaesthesia and continued till the end of the surgery in both the groups. The patients, surgeons, and nurses involved in the recording of nasopharyngeal temperature (NPT) were unaware of the drug infused.
All the patients were fasting 8 hours before the surgery and were premedicated with alprazolam 0.25 mg on the night before and the morning of surgery. On arrival to the preoperative holding area, the patients were connected to a pulse oximeter, their non-invasive blood pressure was measured, and electrocardiography was performed (CARESCAPE™ monitor B850 attached to Anaesthesia work station Avance CS^2). Core body temperature was measured using a calibrated nasopharyngeal thermocouple (GE Healthcare Systems, Germany). The length of probe placement was measured and marked from the nostril to the tragus of the ipsilateral ear (mostly 10–14 cm), and the probe was placed after application of local anaesthesia with 2% lignocaine jelly. A baseline temperature recording before the start of the infusion was noted. An 18-G peripheral intravenous cannula was secured, and the infusion (prepared by anaesthesia technician) was started depending on the group assigned. After 1 hour of administration of the infusion, the patient was shifted into the operating room and premedicated with glycopyrrolate 0.2 mg and fentanyl 2 µg kg^{-1} injections. Preoxygenation was performed for 3 min, and the patients were induced with thiopentone 4 mg kg^{-1} and atracurium 0.5 mg kg^{-1}. Intubation was followed by prone positioning of the patient, and confirmation of nasopharyngeal probe placement with the mark was performed. Intraoperative maintenance was performed with oxygen and air in 1:1 ratio and isoflurane 0.7–1.2 MAC using closed circuit (AvanceCS^2, GE Healthcare system, Germany). Atracurium was infused at a rate of 4 µg kg^{-1} min^{-1}. Throughout the procedure, ambient operating room temperature was maintained at approximately 23°C. In the intraoperative period, both the groups received lactated Ringer's solution at the rate of 2 mL kg^{-1} h^{-1} maintained at an ambient temperature along with the infusions assigned. The patients were covered with a sheet, and the irrigating fluids used were also maintained at an ambient temperature. At the end of the procedure, the patients were extubated after reversal of neuromuscular blockade per the routine protocol, and the infusion of the study drugs was stopped. No other warming device or technique was used as the procedure time was less than 2.5 h.

NPT, heart rate, systolic and diastolic blood pressure, and oxygen saturation were noted just before the onset of infusion, every 15 min after that until the end of the operation, and then every 30 min for 2 h after extubation. The patients were monitored for shivering in the postoperative period by an independent observer using a scoring system (0: no shivering, 1: no visible muscle activity but piloerection, 2: muscular activity in 1 muscle group, 3: moderate muscular activity in more than 1 muscle group, and 4: violent muscular activity that involves the whole body). Patients with a score of 2 or more were treated with tramadol 50 mg injection, and the number of such doses was noted. Duration of anaesthesia, surgery, and nephroscopy and the amount of intravenous fluid and irrigating fluid used were noted. The total leucocyte count and serum creatinine and electrolyte levels were noted

Main Points:

- Thermal discomfort following endoscopic urologic procedures is tremendous and more stressful in the postoperative period.
- Administration of aminoacids promotes five fold higher heat production in anesthetised patients than in awake.
- Lower dose of aminoacids(60ml/hr) administration in the perioperative period produces controlled decrease in temperature and reduced incidence of shivering in PCNL.

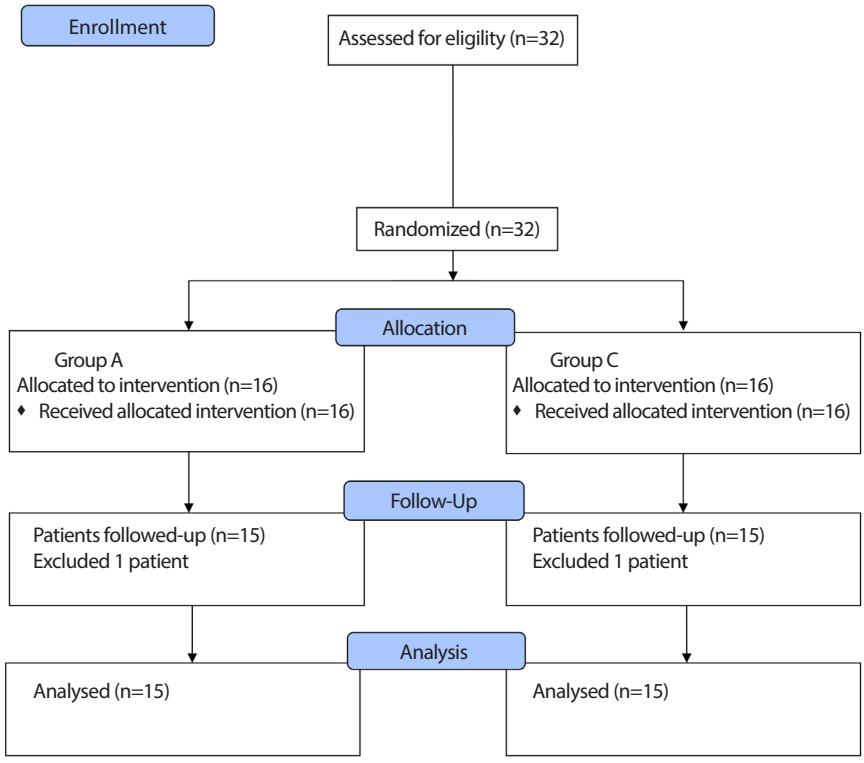

Figure 1. Flow diagram

preoperatively, on the day of surgery and on the first postoperative day. Incidence of fever and bleeding and duration of hospital stay were also recorded.

A total of 16 patients were enrolled in each group. Sample size calculation was performed using power/sample size calculator (ww.stat.ubc.ca) from the data of a previously published study, which reported a significantly higher core temperature in the AA-treated group (mean decrease in temperature: 1.7°C±0.8°C) than the control group (mean decrease in temperature: 1.1°C±0.1°C) with 80% power and 0.05 significance (12).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software version 17 (IBM SPSS Corp.; Armonk, NY, USA). Continuous variables were compared using independent sample t-test. Categorical variables were compared using the chi-square test. A 2-sided *P* less than 0.05 was considered significant for all tests.

Results

A total of 16 patients were enrolled in each group; 1 patient in group A was excluded owing to bleeding and transfusion of a large volume of fluid, and 1 patient in group C was excluded because of hypotension suspected to be secondary to urosepsis.

Demography

Patients in the 2 groups were comparable with respect to demographic variables, such as age, sex, weight and height, as represented in Table 1. In the intraoperative period, the anaesthetic management was similar in both the groups. This is represented in Table 2 as shown by the duration of anaesthesia, surgery, and nephroscopy and the amounts of intravenous fluids and irrigating fluids used.

Intraoperative nasopharyngeal temperature

The baseline NPT was 36.37°C in group A and 36.23°C in group C. NPT decreased in both the groups with induction of anaesthesia. Although the decrease in NPT was more in group C than in group A, there was no statistically significant difference at various measurement points during the intraoperative period. The details of intraoperative NPT are given in Table 3.

Postoperative nasopharyngeal temperature

The NPT continued to decrease in both the groups in the postoperative period. There was a significant difference in the temperature among the 2 groups at 30, 60, and 120 min postoperatively (Table 4). The decrease in NPT postoperatively was significantly less in group A than in group C.

Table 1. Demographic Characteristics of the Patients

Demographic profile	Group A (n=15), mean±SD	Group C (n=15), mean±SD	*P*
Age (y)	41.3±7.37	44.9±10.61	0.308
Sex (men: women)	10:5	12:3	0.463
Weight (kg)	63.4±6.8	65.2±7.63	0.332
Height (cm)	162.4±6.6	165.4±8.5	0.625

SD: standard deviation

Table 2. Intraoperative Details of the Patients in Groups A and C

Intraoperative data	Group A (n=15), mean±SD	Group C (n=15), mean±SD	*P*
Duration of anaesthesia (min)	155.67±38.72	147.67±30.69	0.536
Duration of surgery (min)	138.00±36.68	120.80±28.52	0.163
Duration of nephroscopy (min)	83.40±18.13	88.60±25.04	0.520
Amount of intravenous fluids (mL)	1146.6±424.0	1100.0±387.2	0.755
Amount of irrigation fluids (L)	26.53±9.81	25.00±11.71	0.701

SD: standard deviation

Table 3. Intraoperative Nasopharyngeal Temperature Recordings in Groups A and C

Variables	Group A (n=15)	Group C (n=15)	*P*
Temp baseline, °C	36.37±0.36	36.23±0.17	0.192
Temp induction, °C	36.16±0.42	35.99±0.26	0.166
Temp post-induction, °C	36.00±0.50	35.82±0.36	0.268
Temp 30 min, °C	35.90±0.49	35.66±0.41	0.224
Temp 45 min, °C	35.74±0.54	35.48±0.44	0.165
Temp 60 min, °C	35.68±0.63	35.38±0.46	0.151
Temp 75 min, °C	35.66±0.77	35.30±0.48	0.134
Temp 90 min, °C	35.62±0.85	35.21±0.53	0.128
Temp 105 min, °C	35.59±0.94	35.09±0.59	0.119
Temp 120 min, °C	35.40±0.93	35.18±0.66	0.528
Temp 135 min, °C	35.30±1.01	35.25±0.71	0.890
Temp 150 min, °C	35.12±1.04	34.95±0.34	0.704
Temp 165 min, °C	35.23±0.94	34.96±0.05	0.651

Temp: temperature

Postoperative shivering

Only 2 patients of 15 experienced shivering in the AA group, whereas 11 of 15 patients experienced shivering in the control group at extubation (Table 5).

Table 4. Nasopharyngeal Temperature Recordings Postoperatively in Groups A and C

	Group A (n=15)	Group C (n=15)	*P*
Temp extubation, °C	34.62±0.96	34.24±0.52	0.193
Temp 30 min, °C	34.31±0.82	33.66±0.87	0.047*
Temp 60 min, °C	34.74±0.68	33.74±0.68	0.049*
Temp 90 min, °C	34.50±0.85	34.05±0.63	0.111
Temp 120 min, °C	34.86±0.85	34.24±0.65	0.036*

*p<0.05 (statistically significant); Temp: temperature

Table 5. Number and Grade of Shivering at Extubation in Group A and C

Shivering score	Group A (n=15)	Group C (n=15)
0	13	4
1	0	3
2	0	2
3	1	5
4	1	1

Complications

Of the patients, 1 in each group received 1 transfusion of packed cells in the postoperative period. None of the patients in either group had sepsis or shock. Leucocytosis was present in almost all the patients in both the groups, but this did not manifest in an increased incidence of fever. The mean duration of hospital stay in group A was 7.812 and in group C was 7.53 days (Table 6).

Discussion

Major perioperative complications of PCNL include hypothermia, bleeding, and sepsis. Several studies have reported the drop in temperature to as low as 35°C because of prolonged duration of surgery and continuous irrigation of pelvicalyceal system.[13] This increases the risk of patients developing complications secondary to hypothermia, such as bleeding and delayed recovery. Hypothermia also causes shivering in the postoperative period. In a recent study, thermal discomfort associated with shivering in the awakening period was considered by patients as the worst and most stressful experience of the entire hospital stay.[14] Measures used to prevent hypothermia predominantly restrict heat loss but do not address the decrease in basal metabolism seen with anaesthesia. AAs, by increasing oxidative metabolism and heat generation, have been found to attenuate perioperative hypothermia in patients undergoing major abdominal surgeries, such as colorectal surgeries and hysterectomies.[7-11] The exact mechanism of AA-induced thermogenesis is not known, but

Table 6. Complications in Groups A and C

Complications	Group A (n=15)	Group C (n=15)
Leucocytosis (>10,000 mL^{-1})	12	13
Fever	2	1
Blood transfusion	1	1
Sepsis/shock	0	0
Duration of hospital stay (mean number of days)	7.812	7.53

both protein synthesis and breakdown (for gluconeogenesis and ureagenesis) are thought to be causative. In unanaesthetised patients, nearly half of the heat is generated primarily in the splanchnic tissues because of the processing of AAs in the liver.[14] Under anaesthesia, there is a decrease in the hepatic capacity of AA processing, and approximately 75% of thermogenesis occurs in the extra splanchnic tissues, mainly the skeletal muscle.[15] The increase in protein synthesis in the skeletal muscle is postulated to be owing to insulin-mediated activation of translation initiation regulators.[16] As the skeletal muscles form the largest proportion of the body mass, heat production in muscles significantly attenuates hypothermia. There seems to be a synergy for heat production between anaesthesia and AA administration.

Heat generation was 5-fold more in anaesthetised patients than in awake patients. In awake patients, the central thermoregulatory centres inhibit heat production owing to AA. Under anaesthesia, the action of these centres is lowered and heat production in the skeletal muscle occurs unopposed. Many studies have found that heat production predominantly occurs at emergence from anaesthesia rather than intraoperatively. The stress associated with recovery from anaesthesia stimulates sympathetic nervous output. This sympathetic surge along with AA-induced thermogenesis is postulated to cause substantial increase in heat production at extubation.

In this study, the decrease in temperature during the initial phase of anaesthesia reflecting redistribution of heat was not prevented by preoperative infusion of AA. Redistribution along with continuous irrigation of the pelvicalyceal system resulted in a drop in the temperature in both the groups in the intraoperative period. The drop in group A was gradual over a period and less compared with that in group C, although the difference did not show any statistical significance (Table 3).

In the postoperative period as well, patients in the control group had significantly lower NPT than those in the AA-treated group. Only 2 patients in group A had shivering postoperatively compared with 11 in the control group. We believe that irrigation of the pelvicalyceal system not only caused intraoperative hypothermia but also led to continued decrease in the temperature postoperatively. The accelerated heat production at extubation owing to the mechanisms described earlier helped to preserve the temperature better in patients who received AAs. This resulted in non-shivering and comfort in patients in group A in the postoperative period. It is important that the incidence of shivering is reduced, as shivering by itself is not very efficient in raising the body temperature and is very unpleasant to the patients.

The dose, composition, and duration of AA infusion are important. The magnitude of the thermogenic response is dose dependent and presence of branched chain AAs in the composition is requisite. In this study, branched AAs were used, but the dose (60 mL h^{-1} corresponding to 100 KJ h^{-1}) was low compared with other studies (126 mL h^{-1} corresponding to 240 KJ h^{-1}).[7,8] The lower dose was chosen because many patients have obstructive renopathy despite normal renal parameters, and their response to a nitrogen load is not known.

Postoperative creatinine and urea levels were monitored, and there was no significant increase from the baseline. There are no known contraindications for the use of AAs, although caution needs to be exercised in patients with abnormal pulmonary function as the increased oxygen consumption increases ventilator demands.

In this study, we used nasopharyngeal probe in the perioperative period as it is commonly used; recommended sites[17] for continuous temperature measurement were chosen with much lesser patient discomfort even when awake. The depth of nasopharyngeal probe is more than 10 cm when the distance between the tragus and the ala of nostril is measured, which is closest to the internal carotid artery at upper or mid nasopharynx.[18,19]

Conclusion

Intravenous administration of AAs attenuated postoperative hypothermia and reduced shivering in patients undergoing PCNL without any adverse effects.

Ethics Committee Approval: Ethics committee approval was received for this study from the NIMS Institutional Ethics Committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – I.G.; Design – K.J.; Supervision – P.D.; Resources – I.G., K.J.; Materials – P.D.; Data Collection and/or Processing – I.G., M.P.; Analysis and/or Interpretation – K.J., I.G., M.P.; Literature Search – M.P., K.J.; Writing Manuscript – I.G., M.P.; Critical Review – I.G., K.J., M.P., P.D.; Other – K.J., M.P., P.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

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References

1. Leaper DJ, Tanner J, Kiernan M, Assadian O, Edmiston CE Jr. Surgical site infection: poor compliance with guidelines and care bundles. *Int Wound J.* 2015; 12: 357-62. [Crossref]
2. Esnaola NF, Cole DJ. Perioperative normothermia during major surgery: is it important? *Adv Surg.* 2011; 45: 249-63. [Crossref]
3. Díaz M, Becker DE. Thermoregulation: Physiological and Clinical Considerations during Sedation and General Anesthesia. *Anesth Prog.* 2010; 57: 25-33. [Crossref]
4. John M, Ford J, Harper M. Peri-operative warming devices: performance and clinical application. *Anaesthesia.* 2014; 69: 623-38. [Crossref]
5. Yamaoka I. Modification of core body temperature by amino acid administration. *Asia Pac J Clin Nutr.* 2008; 17: 309-11.
6. Kasai T, Nakajima Y, Matsukawa T, Ueno H, Sunaguchi M, Mizobe T. Effect of preoperative amino acid infusion on thermoregulatory response during spinal anaesthesia. *BJA.* 2003; 90: 58-61. [Crossref]
7. Sellden 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.* 1994; 86: 611-8. [Crossref]
8. Sellden E, Branstorm R, Brundin T. Preoperative infusion of amino acids prevents postoperative hypothermia. *BJA.* 1996; 96: 227-34. [Crossref]
9. Fujita Y, Yamaguchi S, Nakamura K, Horiguchi Y, Ikeda D, Kaneko M, et al. Effect of amino acid and glucose infusion on perioperative body temperature and postoperative infection in patients undergoing total knee arthroplasty. *Masui.* 2012; 61: 68-73.
10. 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. [Crossref]
11. Inoue S, Shinjo T, Kawaguchi M, Nakajima Y, Furuya H. 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 controlled trial. *J Anaesth.* 2011; 25: 850-4. [Crossref]
12. Sellden E, Lindahl SG. Postoperative nitrogen excretion after amino acid-induced thermogenesis under anaesthesia. *Anaesth Analg.* 1998; 87: 641-6. [Crossref]
13. Tekgul ZT, Pektas S, Yildirim U, Karaman Y, Cakmak Y, Ozkarakas H, et al. A prospective, randomized, double blind study on the effects of the temperature of irrigation solutions on thermoregulation and postoperative complications in percutaneous nephrolithotomy. *J Anaesth.* 2015; 29: 165-9. [Crossref]
14. Brundin T, Wahren J. Effect of i.v aminoacids on splanchnic and whole body oxygen consumption, blood flow and body temperatures. *Am J Physiol.* 1994; 266: 396-402. [Crossref]
15. Sellden E, Branstorm R, Brundin T. Augmented thermic effect of amino acids under general anaesthesia occurs predominantly in extra-splanchnic tissues. *Clin Sci (Lond).* 1996; 91: 431-9. [Crossref]
16. Yamaoka I, Doi M, Nakayama M, Ozeki A, Mochizuki S, Sugahara K, et al. intravenous administration of amino acids during anaesthesia stimulates muscle protein synthesis and heat accumulation in the body. *Am J Physiol Endocrinol Metab.* 2006; 29: E882-8. [Crossref]
17. Torossian A; TEMMP (Thermoregulation in Europe Monitoring and Managing Patient Temperature) Study Group. Survey on intraoperative temperature management in Europe. *Eur J Anaesthesiol.* 2007; 24: 668-75. [Crossref]
18. Lee J, Lim H, Son KG, Ko S. Optimal nasopharyngeal temperature probe placement. *Anesth Analg.* 2014; 119: 875-9. [Crossref]
19. Wang M, Singh A, Qureshi H, Leone A, Mascha EJ, Sessler DI. Optimal Depth for Nasopharyngeal Temperature Probe Positioning. *Anesth Analg.* 2016; 122: 1434-8. [Crossref]