Thermoregulatory Response to Aminoacid Infusion during Spinal Anaesthesia

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Abstract: *Background*: Perioperative hypothermia is a common and a major problem in general anaesthesia and neuraxial anaesthesia. Preoperative infusion of amino acids (AA)s is known to prevent perioperative hypothermia during general anaesthesia. We tested the hypothesis that AA infusions given *via* the intravenous route would also cause thermogenic stimulation under spinal anaesthesia.

Methods: Eighty patients undergoing transurethral tumour resection under spinal anaesthesia were divided into two groups: AA infusion (AA group) starting 1 h before surgery and continued during surgery; saline infusion (control group). The temperature in the tympanic membrane was recorded immediately before infusion commencement and continued throughout anaesthesia. Sensory block level and haemodynamic parameters were recorded during anaesthesia. Postoperative shivering was assessed in postoperative care unit.

Results: Body core (T_{core}) values decreased during the study period in comparison with baseline values in the control group. The AA group had significantly higher T_{core} values during anaesthesia and surgery compared with the control group. Mean sensory block level and haemodynamic parameters were comparable between the two groups. Shivering occurred significantly more frequently in the control group than in the AA group.

Conclusion: AA infusions can prevent spinal anaesthesia-induced hypothermia without any effects on sensory block level and haemodynamics.

Keywords: Anaesthesia, spinal, aminoacid, thermoregulatory.

INTRODUCTION

Perioperative hypothermia (PH) is a common and major problem in general anaesthesia and neuraxial anaesthesia. PH is associated with an increased incidence of cardiovascular, hemorrhagic and infectious complications that can adversely affect final outcome in surgical patients [1-3]. Hypothermia also causes postoperative shivering, and may increase morbidity and mortality by causing elevated oxygen consumption and arterial hypoxaemia [4,5]. General anaesthesia and neuraxial anaesthesia markedly affect thermal homeostasis by influencing central thermoregulation mechanisms, reducing sympathetic tone with inhibition of peripheral vasoconstriction and consequent redistribution of body heat from the core to peripheral compartments [6].

Administration of proteins or amino acids (AA)s enhances thermogenesis, presumably by stimulating oxidative metabolism. AAs also alter central thermoregulatory control [7,8]. Studies have supported the notion that anaesthesia-induced hypothermia can be prevented by intravenous infusion of AAs, mostly as a result of increases in heat production and energy expenditure as well as neuraxial anaesthesia [9-13]. However, studies in spinal anaesthesia are very few compared with those focusing on general anaesthesia.

Here, we compared the effects of intraoperative administration of AA solutions on intraoperative hypothermia and postoperative shivering in patients undergoing spinal anaesthesia. We also studied the effects of AA solutions on haemodynamics and sensory block level.

METHODS

The study protocol was approved by the Medical Ethics Committee of Sisli Etfal Training and Research Hospital (Istanbul, Turkey). All patients were informed about the study protocol and the risks before providing their consent to participate.

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Eighty patients with physical status II-III according to the American Society of Anesthesiologists (ASA) undergoing transurethral tumour resection were the study cohort in this prospective, randomised study. None of the patients were obese, febrile or taking vasoactive drugs, or had any history of endocrine disease. Patients with contraindications to spinal anaesthesia, or who refused to have spinal anaesthesia, were excluded from the study.

Baseline measurements of temperature, blood pressure (BP) and heart rate (HR) were recorded before the infusion of AAs or fluids were started. A 20-G catheter was inserted in an antecubital vein for the administration of AA solution. Another 20-G catheter was placed in a contralateral antecubital vein for fluid infusion. In all patients, nutrient-free Ringer's acetate solution was infused at 8 ml/kg/h during surgery. Intravenous fluids and irrigation solutions given to patients were at room temperature. Patients were assigned randomly into two groups of 40: an AA infusion group (AA group) and a saline infusion group (control group). In the AA group, a balanced mixture of 20 amino acids (Primene 10%; Eczacibasi-Baxter, Istanbul, Turkey) was infused at 2 ml/kg/h. These infusions were given 1 h before the induction of anaesthesia and continued during anaesthesia and surgery. Results were compared with those from the control group receiving the same amount of nutrient-free physiological (0.9%) saline solution. Temperature recording was started immediately before the onset of infusion of AA/saline solution and continued throughout anaesthesia.

HR, non-invasive arterial BP, peripheral oxygen saturation, and electrocardiography (ECG) were monitored continuously with a KMA-175 Monitor (Petas, Istanbul, Turkey). A dedicated observer recorded these parameters: before spinal anaesthesia; every 1 min for 15 min after spinal anaesthesia; every 3 min thereafter for 30 min; and every 5 min until the end of surgery. Core temperature (T_{core}) was measured using a cotton-tipped probe positioned adjacent to the tympanic membrane. The external auditory channel was packed with cotton for insulation.

Room temperature was maintained at 21-23°C. The anaesthesia protocol was standardised. Patients received midazolam (1 mg, i.v.) before spinal anaesthesia. In both groups, spinal anaesthesia was undertaken by one anaesthesiologist using the same method with the patient in the lateral position using a midline approach at L_3-L_4 or L_4-L_5 with a 25-G Quincke needle. After observation of the free flow of cerebrospinal fluid, patients received 2.5ml 0.5% levobupivacaine + 25µg fentanyl. Sensory blockade was monitored using the pin-prick test at 1-min intervals for the first 5 min, then every 2 min for 20 min, until the end of surgery. Surgery was allowed if the upper dermatome to the level of the loss of discrimination to a pin-prick was at least T_{10}. Maximum block level was recorded.

Postoperative shivering was assessed in the postoperative care unit by another anaesthesiologist who was unaware of what the patients received according to the classification shown in Table **1** [14].

Table 1: Grading of Shivering [14]

Grade Definition	
Grade 0	No shivering
Grade 1	No visible muscular activity. Piloerection or peripheral cyanosis present
Grade 2	Muscular activity in a single muscle group
Grade 3	Moderate muscular activity in more than one muscle group. No generalized shivering
Grade 4	Generalized shivering

Statistical Analyses

Sample size was calculated as a minimum of 30 patients (based on our preliminary results) to provide 80% power and α=0.05 to detect a mean difference in T_{core} of 0.7°C between the two groups. We studied 40 patients to account for possible dropouts. Results are mean ± standard deviation or median range for ordinal data. Changes in measured parameters were assessed using analyses of variance (ANOVA). The Mann-Whitney *U* test was used for non-parametric values. The chi-square test was used to compare frequencies, and $P<0.05$ was considered significant.

RESULTS

There were no significant differences in age, height, weight, ASA grade or duration of surgery between the two groups (Table **2**).

Baseline T_{core} was comparable between the two groups. T_{core} values decreased during the study period in comparison with baseline values in the control group ($P<0.05$) (Table **3**). The AA group had significantly higher T_{core} values during anaesthesia and surgery compared with the control group (Table **3**). Mean final

T_{core} 60 min after the induction of spinal anaesthesia was ≈35.2°C in the control group and 36.4°C in the AA group (P<0.05).

Table 2: Demographic Data and Duration of Anaesthesia

	Grup AA	Grup C
Age (years)	50.83 ± 5.84	50.75 ± 5.85
Weight (kg)	75.95 ± 8.37	78.55 ± 7.67
Height (cm)	171.75 ± 4.17	171.95 ± 2.90
ASA II/III (n)*	31/9	30/10
Duration of surgery (min)	62.40± 6.64	59.92± 5.58

Data are expressed as mean ± standard deviation, * numbers

Table 3: Tympanic Membrane Temperatures of the Groups

Time	Grup AA	Grup C
Before infusion (Baseline)	36.96 ± 0.010	36.74 ± 0.010
At the end of the infusion	37.38 ± 0.012	36.54 ± 0.012
After spinal anaesthesia	37.03 ± 0.010	36.11 ± 0.010
Intraoperative 10.min	36.93 ± 0.011	35.82 ± 0.011*/‡
Intraoperative 20.min	36.46 ± 0.009	35.69 ± 0.009*/‡
Intraoperative 30.min	36.42 ± 0.007	35.22± 0.007*/‡
Intraoperative 60.min	36.37 ± 0.011	35.18 ± 0.009*/‡

Data are expressed as mean ± standard deviation. (*p<0.05 Compared to baseline values, ‡ p<0.05 Compared to group AA)

The mean height of spinal anaesthesia (as assessed by the pin-prick test) was at dermatome level T_{10} in both groups (P>0.05). In the AA group, the range was T_8-T_{10} and in the control group it was T_9-T_{10}.

Table 4: Haemodynamic Parameters of the Groups

Time	MAP (mmHg)		HR (beat/min)	
	Grup AA	Grup C	Grup AA	Grup C
Before infusion (Baseline)	92.92 ± 1.94	96.25 ± 2.01	71.67 ± 7.79	72.40 ± 7.81
At the end of the infusion	92.65 ± 2.04	95.15 ± 1.93	71.12 ± 7.94	72.05 ± 7.61
After spinal anaesthesia	93.67 ± 1.95	95.27 ± 2.03	72.12 ± 7.61	71.85 ± 7.14
Intraoperative 10 min.	93.15 ± 1.86	95.77 ± 1.92	71.62 ± 7.00	70.85 ± 7.28
Intraoperative 20 min.	93.1 ± 1.76	95.02 ± 1.84	71.04 ± 7.12	70.60 ± 6.92
Intraoperative 30 min.	92.62 ± 1.91	94.40 ± 1.82	70.72 ± 6.59	70.12 ± 7.08
Intraoperative 60 min.	92.00 ± 1.89	94.82± 1.81	70.12 ± 6.90	69.45 ± 6.84

Data are expressed as mean ± standard deviation

Changes in mean arterial BP and HR did not differ significantly between the groups during the study period (P>0.05) (Table **4**).

The control group had a significantly higher prevalence and degree of shivering compared with the AA group (P<0.05) (Table **5**).

Table 5: Grades of Shivering in the Groups

Grade	Grup AA	Grup C
Grade 0	31 (77.5%)	23 (57.5%)*
Grade 1	5 (12.5%)	7 (17.5%)
Grade 2	3 (7.5%)	6 (15%)
Grade 3	1 (2.5%)	2 (5%)
Grade 4	0	2 (5%)

Data are expressed as numbers (%) (*p<0.05 Compared to group AA)

DISCUSSION

In the present study, AA infusion given before and during anaesthesia and surgery, reduced the prevalence of hypothermia and shivering in patients undergoing spinal anaesthesia. Haemodynamics and sensory block levels were not affected compared with patients not given AA solutions.

Hypothermia is closely related to morbidity during and after surgery. Therefore, prevention of hypothermia is important in the perioperative care of patients undergoing surgery and anaesthesia [15]. Distribution of heat within the body and systemic heat balance affect intraoperative T_{core}. During the first hour of anaesthesia, core-to-peripheral redistribution of heat is the primary cause of core hypothermia [16]. Three major factors contribute towards core hypothermia during neuraxial anaesthesia: internal redistribution of heat from the core of the body to peripheral tissues; heat loss to the environment; inhibition of vasomotor and shivering responses [17,18]. Hypothermia during anaesthesia has largely been accepted to be an inconvenience. Interestingly, in one study, body temperature was monitored in 25% of patients receiving general anaesthesia, but was monitored in only 6% of cases during regional anaesthesia [6]. It is well known that the initial reduction in T_{core} due to heat redistribution from the core to the shell is almost 1°C in the first 40-60 min after the induction of anaesthesia [6, 19]. Accordingly, one can monitor the temperature in all patients undergoing surgical procedures lasting >30 min [6]. Central and peripheral compartments can be used as sites of temperature monitoring [20].

Measurements of temperature in the inner ear, the distal third of the oesophagus, the nasofarinx, and blood are closely related to T_{core} [21]. The nasopharynx is the monitoring site used most often in patients undergoing induction of general anaesthesia, whereas the tympanic membrane is preferred with regional anaesthesia [6] (which we also used). The best monitoring site should be chosen based on the characteristics and site of the surgical procedure the patient is undergoing.

In health, administration of proteins or AAs stimulates resting energy expenditure and increases the metabolic rate to levels above the basal state, thereby stimulating heat production [22,23]. Enteral or parenteral proteins or AA mixtures stimulate oxidative metabolism, typically increasing the metabolic rate by≈20% [24, 25]. Preoperative AA infusion is known to prevent PH during general anaesthesia as a result of increased thermogenesis [9,26]. Yamaoka *et al.* elucidated, after intravenous administration of an AA mixture in rats, the contribution of protein synthesis to the prevention of hypothermia during anaesthesia [12]. They confirmed that administration of an AA mixture during anaesthesia attenuated a marked decrease of T_{core} during anaesthesia. These data suggest that stimulation of protein synthesis in skeletal muscle contributes (at least in part) to attenuation of anaesthesia-induced hypothermia by AA administration. AA administration under anaesthesia contributes to increased heat production and a raised threshold for thermoregulatory vasoconstriction [27]. An additional mechanism by which AA infusion might increase the thermoregulatory set point is *via* metabolites that alter central thermoregulatory control. Alternatively, AA infusion might activate peripheral receptors and, therefore, afferent pathways. This possibility is by no means unprecedented: for example, the pyrogenic effect of many cytokines is mediated *via* the vagus nerve [28]. Nakajima *et al.* concluded that AA infusion synchronously increases the triggering threshold for all major autonomic thermoregulatory defences in humans, which is equivalent to an increase in set point. Therefore, AAs influence peripheral heat production and central thermoregulatory control [8].

It is well established that AA infusions provoke thermogenesis [19,27]. Thermogenesis associated with AA infusions has been shown to help increase metabolic heat production, preserve intraoperative T_{core} [10,27] and to modulate complications associated with hypothermia [11, 29-31]. Sellden *et al.* reported that patients receiving an intravenous infusion of an AA solution during surgery maintained a T_{core} almost 0.5°C higher than those receiving crystalloids [9]. Kasai *et al.* found that AA infusions caused an increase in T_{core}, and that T_{core} values 30 min after administration of an AA infusion were significantly higher than those in a control group which had been given the same volume of nutrient-free standard saline solution [27]. Widman *et al.* found that the reduction in T_{core} was more marked in the control group than in the AA group throughout surgery [29]. T_{core} values were significantly higher in the AA infusion group than those in the saline group in a study by Ali *et al.* [32]. These three studies were undertaken in patients under spinal anaesthesia, as in our study. We also observed significantly lower T_{core} values in our control group compared with the AA group, in accordance with the three studies described above.

One study has shown that AA infusions started at the onset of anaesthesia do not prevent the initial reduction in temperature that occur within the first 20 min of anaesthesia [9]. Studies have demonstrated that prevention of hypothermia is more effective if a peroperative period of AA infusion is included [28,29,32]. Matsukawa *et al.* showed that a rapid decrease in T_{core} resulting mostly from the redistribution of heat from the body core to the peripheral tissues occurs within the first hour after epidural anaesthesia [17]. Kasai *et al.* also mentioned that increases in oxygen consumption as a result of AA infusion are not observed until 1 h after infusion. Therefore, AA infusion starting at the onset of spinal anaesthesia would be less effective than AA infusion starting 1 h or 2 h before the onset of anaesthesia [27]. The decrease in temperature during the initial phase of anaesthesia (probably reflecting heat redistribution within the body) can be prevented by pre-anaesthetic infusions of AAs if infusions are continued during the first hour of anaesthesia [33]. In accordance with those studies, we started AA infusions 1 h before spinal anaesthesia and continued during anaesthesia and surgery.

Other known predictors of hypothermia during spinal anaesthesia are a high spinal block level, 0.15°C for each incremental increase in dermatome level, and advanced age [34]. In our study, the mean age of groups was comparable and mean sensory block was T_{10} in both groups. This result is comparable with the study by Widman *et al.* [29].

In the study by Widman *et al.*, values of systolic BP were similar in the AA group and Ringer's acetate (control) group at the induction of spinal anaesthesia and during surgery [29]. In our study, values of mean arterial BP and HR were not significantly different between AA and control groups, similar to the study by Widman *et al.* Also, our results were consistent with the other two studies in which AA infusions were used for spinal anaesthesia [27,32].

Spinal anaesthesia inhibits thermoregulatory control centrally [35]. However, a far more important effect of neuraxial anaesthesia is the blocking of peripheral sympathetic and motor nerves, which prevents thermoregulatory vasoconstriction and shivering [18,36]. During spinal anaesthesia, sufficient core hypothermia triggers vasoconstriction and shivering in unblocked regions such as the arms [37]. Postoperative shivering is an expression of oxygen debt developed during the intraoperative period. The increased oxygen consumption produced by shivering is unlikely to provoke cardiovascular complications by itself, but it can act as a co-factor in patients with borderline myocardical perfusion. Furthermore, thermal discomfort associated with shivering in the awakening period can be considered as a complication by itself, and is often described by patients as the worst and most stressful experience of the entire hospital stay. It can result in an increase in circulating levels of catecholamines, thereby leading to a higher prevalence of tachycardia and hypertension [38]. The increase in heat production induced by AAs reduces hypothermia and abolishes shivering [11,39]. Shivering occurred on significantly fewer occasions in the AA group than in the control group in the present study. Similar to our study, Ali *et al.* found no generalised shivering in the AA group, whereas in the saline group all patients suffered shivering of varying degrees. Shivering is almost entirely eliminated by normothermia upon awakening irrespective of the method used for maintaining temperature balance, be it from endogenous thermogenesis in response to AAs, as in our study and that of Ali *et al.* [32].

Here, we evaluated the effect of AA infusions on the thermoregulatory response during spinal anaesthesia. We concluded that AA infusions given before and during anaesthesia and surgery restored T_{core} and almost completely eliminated postoperative shivering without significant effects on haemodynamics and sensory block level.

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CONFLICT OF INTEREST

None.

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DISCLOSURE

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