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Research Article

Effect of intrathecal meperidine and intravenous amino acid infusion in reducing intraoperative shivering during spinal anesthesia: A prospective randomized trial ☆

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Abstract *Background:* This is a prospective randomized double blind study to compare the efficacy of intravenous amino acid infusion versus meperidine added to intrathecal hyperbaric bupivacaine in reducing intraoperative shivering in parturient undergoing elective cesarean section under spinal anesthesia.

Methods: Sixty patients were randomly allocated into two groups. Group (A) (Amino-acid) (n = 30) who received 2 ml of 0.5% hyperbaric bupivacaine and ½ ml normal saline 0.9% (total volume 2.5 ml) intrathecal with intravenous administration of amino acids (Aminoven 5%, Fresenius Kabi), infused at rate 3 ml/kg/h with the start of spinal anesthesia and throughout the operation. Group (M) (meperidine) (n = 30) who received 2 ml of 0.5% hyperbaric bupivacaine with 10 mg meperidine in ½ ml volume (total volume 2.5 ml) intrathecal with intravenous administration of normal saline 0.9% at 3 ml/kg/h with the start of spinal anesthesia.

Results: Group (A) showed significantly higher core temperature from 20 to 60 min than group (M) ($p < 0.001$), also the amino acid group (group A) had a significantly higher skin temperature from 10 to 60 min during surgery, and lower shivering score than group (M) ($p < 0.05$), during spinal anesthesia in parturients undergoing cesarean section.

Conclusion: Amino acids infusion decreased the incidence of shivering, increased peripheral and core temperature than intrathecal meperidine, which seems a safer alternative, more effective with lesser side effects than intrathecal meperidine in parturients undergoing cesarean section under spinal anesthesia.

☆ The study was conducted at obstetrics and gynecology teaching hospital of Ain shams university, Cairo, Egypt.

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1. Introduction

Shivering may occur as an adverse effect of surgery and anesthesia. Shivering associated with spinal anesthesia is a frequent event, and the reported median incidence of shivering related to neuraxial anesthesia is up to 55% [1]. The mechanism of shivering in patients undergoing spinal anesthesia is not clear but hypothermia due to redistribution of heat caused by vasodilation below the level of a neuraxial block is suggested. Spinal anesthesia also impairs the thermoregulation system by inhibiting vasoconstriction. Shivering increases oxygen consumption, metabolic rate, lactic acidosis, carbon dioxide production, plasma catecholamines and cardiac output. Shivering movement may interfere with monitoring of hemodynamics as well as increasing patient discomfort and distress. Therefore, it is very important to prevent shivering during spinal anesthesia [2]. Core temperature is maintained within normal limits of 36.5, 37.5 °C [3], even in the presence of an adverse environmental temperature, by a combination of behavioral and physiological responses. Anesthesia abolishes behavioral mechanisms and has the potential to disrupt the physiological mechanisms of thermoregulation. Intraoperative core temperature depends both on distribution of heat within the body and on systemic heat balance. During the first four hours of anesthesia, core-to-peripheral redistribution of heat is the primary cause of core hypothermia [4]. Hypothermia results from heat loss exceeding heat production [5] as anesthetics profoundly impair thermoregulatory control [6,7]. Factors that increase thermogenesis or reduce loss of heat to the environment moderate the rate at which intraoperative hypothermia develops [8–10].

Enteral or parenteral administration of amino acid solution stimulates oxidative metabolism, typically increasing metabolic rate by 20% [11,12]. Thermo-genesis associated with amino acid infusions has been shown in numerous studies to help preserve intraoperative core temperature [8,13] and to moderate complications associated with hypothermia [14–16].

Meperidine possesses special antishivering properties that are not shared by pure μ-receptor opioids. There are many studies for meperidine via intravenous, Intrathecal, and epidural administrations [17]. Possible suggested mechanisms for the antishivering effect of meperidine include κ-opioid receptor activity, anticholinergic action, biogenic monoamine reuptake inhibition, NMDA receptor antagonism or stimulation of α-adrenoceptors [18–21].

This prospective, randomized, double blind study was performed to compare the antishivering effects of intravenous administered amino acid solution versus meperidine added to intrathecal hyperbaric bupivacaine in patients who underwent elective cesarean delivery under spinal anesthesia.

2. Patients and methods

After receiving approval from the ethics committee at obstetrics and gynecology teaching hospital of Ain Shams University and informed written consent from patients, 60 patients (ASA physical status I or II) scheduled for elective cesarean delivery under spinal anesthesia, were enrolled in the study. Patients with contraindications to regional anesthesia, allergy to the study medications, obesity (Body Mass Index (BMI) = 30 kg/m^2, class I and above), preeclampsia, placenta previa or diabetes were excluded.

Patients were divided into two groups by using computer generated random tables with closed sealed envelopes. An assistant who was not involved in the study prepared the medication before giving spinal anesthesia. Heart rate, blood pressure and oxygen saturation monitoring were established. Patients were given intravenous Ringer's solution. Oxygen 3 liters per minute (3 LPM) was administered through nasal prongs during anesthesia. Spinal anesthesia in the sitting position at the L_{3-4} interspace with a midline approach uses 25 G or 27 G Quincke needle. In group A (Amino-acid group, $n = 30$), Spinal anesthesia consisted of 2 ml of 0.5% hyperbaric bupivacaine + ½ ml. of normal saline 0.9%, total volume 2½ ml, together with intravenous administration of Aminoven 5%, Fresenius Kabi, (that can be given in a peripheral venous access) at a rate of 3 ml/kg/h, while, Group M (meperidine group $n = 30$), received 2 ml of 0.5% hyperbaric bupivacaine, plus 10 mg pethidine in ½ ml volume, total volume 2½ ml. intrathecal, together with intravenous administration of normal saline 0.9% at a rate of 3 ml/kg/h. After giving spinal anesthesia, patients were positioned supine with a wedge beneath the right hip to maintain a pelvic tilt of 30°. Sensory levels were determined by pinprick and the motor blockage was evaluated using Bromage's criteria. Core temperature was measured from the rectum where the rectal probe was inserted during urinary bladder catheterization of the patient and skin temperature was taken from the forehead before establishing regional anesthesia as baseline and at 10 min interval. Shivering was recorded during surgery and in the recovery room by a blind observer. Shivering was graded on a scale:

- 0 = no shivering.
- 1 = piloerection or peripheral vasoconstriction but no visible shivering.
- 2 = muscular activity in only one muscle group.
- 3 = muscular activity in more than one muscle group but not generalized shivering.
- 4 = shivering involving the whole body [22].

The operating room temperature was maintained at 23–25 °C, and perioperative side effects including pruritus, sedation, nausea and vomiting were recorded.

3. Statistical analysis

Analysis of data was done by using SPSS (statistical program for social science version 16) where, quantitative variables were expressed as mean, SD and range, while qualitative variables as number and percentage. Chi-square test was used to compare qualitative variables between groups, whereas, unpaired *t*-test was used to compare two independent groups as regards quantitative variable. *P* value > 0.05 was considered non-significant, $P < 0.05$ significant, and $P < 0.001$ highly significant.

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4. Results

The study was conducted from May 2014 to February 2015; 60 women participated in the study and all completed the study. Demographic variables were similar in both groups, ($p > 0.05$) (Table 1).

Group (A) showed significantly higher core temperature from 20 to 60 min than group (M) ($p < 0.001$) (Table 2).

Also the amino acid group (group A) had a significantly higher skin temperature from 10 to 60 min during surgery, and lower shivering score than group (M), during spinal anesthesia in parturients undergoing cesarean section ($p < 0.05$) (Tables 3 and 4).

The incidence of side-effects in the form of nausea and vomiting, sedation and **pruritus** was not statistically significant among both groups ($p > 0.05$) (Table 5). As well, there were no statistically significant differences between the two groups as regards the neonatal outcomes ($p > 0.05$) (Table 6).

5. Discussion

Spinal anesthesia decreases the vasoconstriction and shivering thresholds to a certain degree [23] because local anesthetics have no thermoregulatory effects [24]. The mechanism of this disturbance during regional anesthesia is unknown but is consistent with thermoregulatory impairment caused by the effects of the regional block upon afferent thermal information. Hypothermia is associated with shivering and excessive sympathetic nervous system stimulation [25], metabolic acidosis, platelet activity is impaired [26] and there is prolongation of the coagulation time and decreased clot formation rate [27,28]. Impaired immune function and delayed wound healing have been demonstrated [29,30].

In our study we compared intravenous amino-acid infusion – Aminoven 5% – to intrathecal meperidine, as regards efficacy in aborting or reducing shivering in parturient undergoing cesarean section under spinal anesthesia. It was found that intravenous amino acid infusion during spinal anesthesia elevates core and skin temperature and decreases shivering rate more than intrathecal meperidine administration, which seems a safer alternative, more effective and lesser side effects than intrathecal meperidine; yet, further studies are recommended

Table 1 Comparison between both groups as regards demographic data.

Variables	Group A ($n = 30$)	Group M ($n = 30$)	*P*-value
Age (years)	30.4 (4.1)	30.8 (3.2)	(0.89) NS
Weight (kg)	72.8 (6.1)	78.2 (4.7)	(0.35) NS
Height (cm)	158.4 (5.3)	160.1 (3.2)	(0.66) NS
Gestational age (weeks)	38.8 (1.1)	39.0 (1.2)	(0.70) NS
Surgery time (min)	62.4 (7.2)	60.2 (8.1)	(0.40) NS
Ambient OR temperature (°C)	23.9 (0.87)	24.3 (1.1)	(0. 123) NS

Data were expressed as mean (SD), $P > 0.05$ non-significant.

Table 2 Comparison between both groups as regards core temperature.

Time after spinal anesthesia	Group A ($n = 30$)	Group M ($n = 30$)	*P*-value
0	36.4 ± 4.1	36.9 ± 5.1	(0.83) NS
10 min	36.2 ± 5.3	35.8 ± 7.2	(0.70) NS
20 min	35.9 ± 7.1 ↑	35.2 ± 4.2	(0.04) S
30 min	35.5 ± 6.2 ↑	34.9 ± 5.1	(0.02) S
40 min	35.2 ± 3.1 ↑	34.5 ± 2.8	(0.002) S
50 min	35.3 ± 4.2 ↑	34.4 ± 3.6	(0.001) S
60 min	35.0 ± 3.1 ↑	34.2 ± 1.5	(0.01) S

Data were expressed as mean ± SD, $P > 0.05$ is non-significant, $P < 0.05$ significant, while $P < 0.001$ is highly significant.

Table 3 Comparison between both groups as regards skin temperature.

Time after spinal anesthesia	Group A ($n = 30$)	Group M ($n = 30$)	*P*-value
0	35.5 ± 2.1	35.2 ± 4.1	(0.78) NS
10 min	35.2 ± 3.1 ↑	34.8 ± 7.2	(0.05) S
20 min	35.0 ± 8.1 ↑	34.7 ± 6.1	(0.04) S
30 min	34.8 ± 5.1 ↑	34.2 ± 3.2	(0.04) S
40 min	34.5 ± 6.2 ↑	33.8 ± 4.1	(0.002) S
50 min	34.2 ± 5.3 ↑	33.5 ± 6.2	(0.01) S
60 min	33.9 ± 1.2 ↑	33.2 ± 3.1	(0.02) S

Data were expressed as mean ± SD, $P > 0.05$ is non-significant, $P < 0.05$ significant, while $P < 0.001$ is highly significant.

Table 4 Comparison between both groups as regards shivering score.

Time passed after spinal anesthesia	Group A (n = 30)	Group M (n = 30)	X^2	P-value
0	0	0	–	–
10 min	0	0	–	–
20 min			5.3	(0.02) S
0	20(66.7%)	17(56.7%)		
1	4(13.3%)	5(16.7%)		
2	6(20%)	8(26.7%)		
30 min			5.7	(0.001) S
0	15(50%)	10(33.3%)		
1	5(16.7%)	9(30%)		
2	5(16.7%)	6(20%)		
3	5(16.7%)	5(16.7%)		
40 min			4.3	(0.04) S
0	12(40%)	8(26.7%)		
1	6(20%)	7(23.3%)		
2	6(20%)	10(33.3%)		
3	6(20%)	5(16.7%)		
50 min			4	(0.05) S
0	10(33.3%)	8(26.7%)		
1	9(30%)	7(23.3%)		
2	6(20%)	10(33.3%)		
3	5(16.7%)	5(16.7%)		
60 min			3.7	(0.05) S
0	8(26.7%)	8(26.7%)		
1	10(33.3%)	7(23.3%)		
2	7(23.3%)	12(40%)		
3	5(16.7%)	3(10%)		
In the recovery room			6.8	(0.002) S
0	5(16.7%)	2(6.7%)		
1	10(33.3%)	8(26.7%)		
2	8(26.7%)	11(36.7%)		
3	6(20%)	6(20%)		
4	1(3.3%)	3(10%)		

Data were expressed as number percent.
$P > 0.05$ is non-significant, $P < 0.05$ significant, while $P < 0.001$ is highly significant.

Table 5 Incidence of maternal adverse reactions in the first 24 h post-operatively.

Side-effect	Group A (n = 30)	Group M (n = 30)	P-value
Nausea and vomiting (n)	3 (10%)	7 (23.33%)	P = 0.299
Sedation (n)	0 (0%)	1 (3.33%)	P = 0.999
Pruritus (n)	0 (0%)	2 (6.66%)	P = 0. 473

Data are expressed as number (percent %).
$P < 0.05$ is considered significant. $P > 0.05$ is non-significant.

to confirm our hypothesis and to study the effect of amino acid volume load and ammonia production in parturient especially those with hepatic or renal impairment.

Perioperative thermal discomfort is often remembered by patients as the worst aspect of their perioperative experience [31]. Prophylaxis of postoperative shivering with simple pharmacological interventions is possible and clinically effective if the risk of developing postoperative shivering is high.

A novel approach to marinating perioperative normothermia has recently been proposed. An intravenous infusion of an amino acid mixture commenced before and continued during anesthesia was found to stimulate metabolic heat production fivefold compared with the thermogenic effect of amino acids observed in the unanesthetized state. This thermogenesis was associated with an increased body temperature [32] which originated predominantly from the extra-splanchnic circulation [8]. However, the increased temperature was achieved not only by increased non-shivering thermogenesis but also by vasoconstriction, reduced cutaneous heat loss [32,33].

Amino acids thus influence both peripheral and heat production and central thermoregulatory control. Synchronous increase in each of the major autonomic thermoregulatory thresholds suggests an alteration in central thermoregulatory function rather than the summation of individual peripheral actions related to each thermoregulatory defense. The mechanism by which amino acid infusion increases the set point was

Table 6 Neonatal outcomes.

Variable	Group A (n = 30)	Group M (n = 30)	P-value
Weight (g)[a]	3186 ± 376	3287 ± 425	P = 0.334
1-min Apgar[b]	9 (8–9)	9 (8–9)	P = 0.94
5-min Apgar[b]	9 (9–9)	9 (9–9)	–
Umbilical artery[a]			
pH	7.22 ± 0.13	7. 19 ± 0.09	P = 0.303
PO_2	16.97 ± 5.5	18.26 ± 5.2	P = 0.354
PCO_2	52.8 ± 4.6	54.2 ± 5. 1	P = 0.269
HCO_3	23.5 ± 1.9	24.3 ± 1.7	P = 0.091
Admission to NICU (n)[c]	0 (0%)	0 (0%)	NA
Lactation[c] difficulties	2 (6.66%)	1 (3.33%)	P = 0.9995

$P > 0.05$ is considered non-significant.
Data are expressed as
[a] Mean ± SD.
[b] Median and (range).
[c] Number (percent %).

not addressed in the study and remains 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. One potential mediator is the sympathetic nervous system. However, intravenous administration of amino acids solutions to patients causes a normal or even supra normal increase in metabolic rate even though pathway connecting the brain with the peripheral sympathetic nerve pathways to the brain is served in these patients and they typically exhibit low peripheral sympathetic system activity [34].

Meperidine (pethidine) is one of the opioids which is remarkably effective in treating postoperative shivering (25 mg) whether given intravenously or intrathecally [34–36] and is unlikely to induce clinically relevant adverse effects in this low dose.

Roy et al. [37] found that adding pethidine intrathecally does not modify the efficacy of the sensory and motor block or its maximum spread but they reported that pethidine 0.2 mg/kg intrathecally lowers the incidence of shivering during spinal anesthesia.

Hong and Lee [38] reported that 10 mg of prophylactic intrathecal pethidine for cesarean delivery reduced the incidence and severity of shivering much more than 0.2 mg morphine intrathecally.

Nakajima et al. [39] reported that amino acid intravenous infusion increased both metabolic rate and resting core temperature during anesthesia. They contributed this to that it produced a synchronous increase in all major autonomic thermoregulatory defense thresholds.

As a limitation to the study we did not consider the hormonal effect on shivering in pregnant women. Pregnant women have very high circulating concentrations of progesterone. This may account for elevated thresholds [40]. We did not measure progesterone levels in our patients.

Conflict of interest

We have no conflict of interest to declare.

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