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The effects of ephedrine on maternal hypothermia in caesarean sections: a double blind randomized clinical trial

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Abstract. – BACKGROUND: The purpose of the study was to investigate the effect of bolus and the combination of bolus and infusion of ephedrine on maternal hypotermia which are used for treating maternal hypotension under spinal anaesthesia.

PATIENTS AND METHODS: 110 ASA I-II patients who developed maternal hypotension were included into the study. Spinal anaesthesia was performed with 12.5 mg heavy bupivacaine + 15 μg fentanyl. Group I: Ephedrine bolus 5 mg plus ephedrine infusion, Group B: Ephedrine bolus 5 mg plus normal saline infusion. The systolic blood pressure was allowed to range between 20% from baseline values. Ephedrine solution infusion started after hypotension occurred (0.5 mg/minute). The body temperature under 35.5°C was accepted as hypothermia. The newborns' rectal temperature was measured. Moreover, the Apgar scores, umbilical vein-arterial blood gas and acid-base status were evaluated.

RESULTS: In Group I, the body core temperatures which were measured at 9, 18, 33, and 39th minutes were significantly higher than Group B ($p < 0.05$). The prevalence of maternal hypothermia in Group I was significantly lower than the Group B, which were as 65.5% (36/55) and 85.5% (47/55), respectively ($p < 0.05$). In Group I, the newborn rectal temperatures and the total dose of ephedrine were significantly higher than Group B ($p < 0.05$). In Group I, the systolic and mean blood pressures were higher than Group B ($p < 0.05$).

CONCLUSIONS: As a result, we found that combined bolus and infusion of ephedrine for treating maternal hypotension prevents maternal and neonatal hypothermia during caesarean section under spinal anaesthesia compared to bolus administrations alone.

Key Words:
Ephedrine, Maternal hypothermia, Maternal hypotension, Spinal anaesthesia.

Introduction

Spinal anaesthesia is the method of choice for caesarean delivery[1,2]. However, increased occurrence of maternal hypotension[1] and hypothermia[3] associated with spinal anaesthesia is likely to be secondary to sympathetic blockade.

Uterine blood flow is directly dependent on maternal blood pressure and maternal hypotension may have deleterious effects on the fetus. If sustained, it may lead to fetal endangerment and possibility of death[4]. Therefore, maternal hypotension should always be treated. Phenylephrine is recommended as a vasopressor agent in recent years[5-7]. However, in some countries which dont have phenylephrine, ephedrine still have been used.

Despite the shorter duration of anesthesia associated with caesarean delivery, the potential for vasodilation, core-to-peripheral redistribution of body heat, and a resulting state of mild maternal hypothermia exists[8]. Furthermore, it is well known that maternal body temperature is associated with neonatal body temperature[9]. It is well known that ephedrine has thermogenic properties related to its beta stimulating properties. Also the vasoconstriction effect of ephedrine may have prevented the internal core-to-peripheral redistribution of heat. These two possible mechanisms of ephedrine's effect on temperature have previously been described, albeit under general anaesthesia[10]. The effects of ephedrine on maternal hypothermia have not been investigated. Bolus of ephedrine is usually applied in daily practice. However, effectiveness of drug infusion is more effective than bolus dose[11].

Therefore, the purpose of this study was to determine the effect of bolus and combined bolus and infusion doses of ephedrine on maternal hypothermia which were used for treating maternal hypotension under spinal anaesthesia.

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Patients and Methods

Trial Design and Patients

The present study was a single-centre, balanced randomized [1:1], double-blinded, parallel group, phase IV study conducted at Inonu University Hospital (Malatya, Turkey) between May 2010 and December 2010. After institutional approval by the Ethics Committee of Inonu University Hospital (10.2. 2009/N^{o} 08); and obtaining written informed consent, 110 healthy ASA physical status I or II pregnant women presenting for scheduled caesarean delivery under spinal anaesthesia were enrolled. All parturients were between 18 and 40 years of age with a singleton pregnancy. The gestation week longer than 37 weeks scheduled for caesarean delivery were eligible to participate. Patients with preexisting or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, contraindications to spinal anaesthesia and body mass index (BMI) > 40 kg/m^2, otitis, and preoperative temperature ≥ 38°C or ≤ 35.5°C, patients taking calcium channel blockers were excluded.

Randomization and allocation of the patients into intervention groups was performed using computerized numbers (Excel; Microsoft, Remond, WA, USA) by an anaesthesiologist not participating to the trial. Both care providers on the ward and the anaesthesiologists assessing outcomes were blinded to the study groups.

All patients received 10 mg of metoclopramide and 50 mg of ranitidine before being admitted to the operating room, and were administered 10 ml/kg of Ringer lactate solution as initial administration via an 18 gauge IV cannula. Body temperatures (tympanic and axillary temperature) were measured with an ear thermometer (Thermoscan IRT3020; Braun, Kronberg, Germany) and an axillary thermometer. Temperatures were measured, when the patients were admitted to the operation room, before prehydration and after the hydration, before spinal anesthesia, every 3 min after spinal anaesthesia insertion.

The temperature of the operating room was maintained at 22°C. No other warming device was used. All patients were covered with one of the surgical drapes in addition to one layer of cotton blanket. The study period ended when the patient was discharged from the postoperative recovery room.

Spinal anaesthesia was performed at right lateral position (L4-L5 or L3-L4 level) with 25-gauge Quincke needle by an anaesthesiologist did not involved in the study, with a 12.5 mg hyperbaric bupivacaine and 15 mg of fentanyl. Block height was tested using pinprick and the surgery commenced after obtaining a sensory block at upwards of T4 dermatome.

Hypotension was defined as a decrease in systolic blood pressure (SBP) of more than 20% from the baseline values (or 90 mmHg, whichever higher). Baseline values were calculated from three measurements taken on the operation room before anaesthesia. The systolic blood pressure was allowed to range between ± 20% from baseline values. The patients developed hypotension was randomly allocated two groups: The ephedrine bolus group (Group B, n=55) and the combination of bolus and infusion of ephedrine group (Group I, n=55).

The bolus group received 5 mg bolus of ephedrine followed by an infusion of saline, while the combination of bolus and infusion of ephedrine group received 5 mg bolus of ephedrine followed by infusion of ephedrine. Ephedrine solutions were prepared as 3 mg/ml in the infusion group. Ephedrine solution infusion started at 10 ml/h (30 mg/h), after hypotension occurred and if hypotension persisted after 3 minute, 5 mg bolus dose was repeated in the both groups. Then infusion rate was increased to 20 ml/h (60 mg/h). In both groups during persistent hypotension (> 20%) or (70 mmHg, whichever higher) 10 mg bolus of ephedrine and 250 ml of Ringer lactate solution were administered. The amount of ephedrine used for each group was recorded. If arterial blood pressure reached to the baseline level infusion was discontinued.

The body temperature under 35.5ºC was accepted as hypothermia. Shivering was graded using the following scale: 0 = no shivering, 1= one or more of the folowing: piloerection, peripheral vasoconstriction, peripheral cyanosis without other visible muscular activity, 2 = visible muscular activity confined to one muscle group; 3 = visible muscular activity in more than one muscle group; and 4 = gross muscular activity involving the whole body. If the shivering score was ≥ 3, treatment with IV meperidine (20 mg) was considered. Patients were assessed for thermal comfort using a verbal numerical scale: 0 = mm as the worst imaginable cold, 50 mm as thermoneutral, and 100 mm as insufferably hot. Pain intensity during the cesarean delivery was measured using a verbal numerical scale (ranges between 0-100: 0 = no pain and 100 = the worst pain imaginable). If patients developed nausea

and vomiting, 10 mg of metoclopramide was administered intravenously.

Maternal data and observations, including body temperatures, degree of shivering, thermal comfort, pain, nausea, heart rate, systolic and mean arterial blood pressure, and block height were recorded at 3 minutes intervals.

Umbilical arterial and umbilical vein blood were sampled from double-clamped segment of umbilical cord for blood gas analysis immediately after delivery. A paediatrist blinded to group assigment determined Apgar scores at the 1st and 5th minutes after delivery. Additionally rectal temperature measurements were recorded. Maternal pulse rate < 45/min was treated with atropine.

After operation, all the patients were observed in post-op recovery unit minimally for 30 minutes until the spinal block level returned to L_5 or having stabil vital signs. Then they were discharged to obstetrics service.

Statistical Analysis

The SPSS 13.0 program was used to analyze the statistical data (SPSS Inc., Chicago, IL, USA). According to $\alpha = 0.05$, $\beta = 0.05$, and power = 0.95, it was found that for each group at least 47 patients were required to detect a 0.3°C change in maternal temperature. Continuous data are expressed as mean ± SD and categorical data are expressed as number or rate. Shapiro Wilk test was used to determine normal distribution of continuous data. The continuous data showed normal distribution ($p > 0.05$). Comparisons of the continuous data within the groups, such as temperature and hemodynamic variables, were performed with repeated measures of ANOVA followed by paired *t* test with Bonferroni correction for multiple comparisons. Unpaired *t* test or Pearson Chi-Square test and Fisher's exact chi-square tests were used to compare variable between the groups where appropriate. A *p* value of < 0.05 was considered as significant.

Results

162 patients were eligible for the study. Fifty of the patients were not developed hypotension and two patient excluded from the study due to not meeting inclusion criteria. 110 patients completed the study (Figure 1). The maternal demographic and obstetric data and duration of operation were similar between two groups (Table I). Anaesthetic details were summarized in Table II.

Throughout the study, there was no difference between the groups regarding axillary tempera-

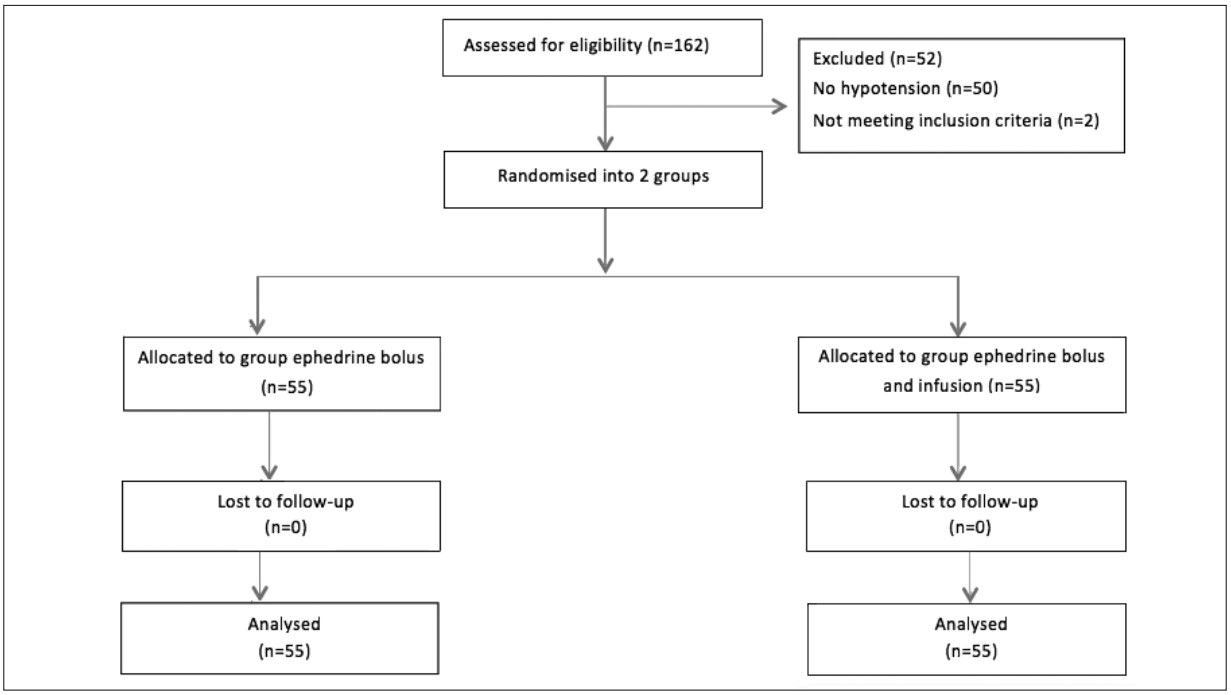

Figure 1. Flow chart of the study.

Table I. Maternal demographic and obstetric data and duration of operation. Values are mean ± SD or median (range).

	Group I (n = 55)	Group B (n = 55)	*p* value
Age (years)	30.3 ± 5.2	29.2 ± 6.3	0.087
Weight (kg)	75.1 ± 15.8	75 ± 11.2	0.096
Height (cm)	160.5 ± 4.5	161 ± 4.1	0.055
Parity (n)	2 (0-6)	1 (0-6)	0.160
Gestation (n)	37.6 ± 2.0	37.6 ± 1.6	0.468
Operation time (min)	43.8 ± 9	43.7 ± 8.9	0.958
Uterine incision delivery (min)	2 (1-3)	2 (1-3)	0.867
Spinal- incision (min)	20 (8-25)	20 (8-25)	0.735
Spinal-delivery (min)	28 (16-35)	28 (15-36)	0.659

tures (Figure 2). The decreases in core temperatures were statistically significant in all groups when compared with baseline level. In Group I, body core temperatures which measured at 9, 18, 33, and 39th minutes were significantly higher than Group B ($p < 0.05$) (Figure 3). The prevalence of hypothermia before and after the baby's birth were significiantly lower in Group I than Group B (Table II). The maternal hypothermia prevalence in Group I was significantly lower than the Group B which were as 65.5% (36/55) and 85.5% (47/55) ($p < 0.05$), respectively. In Group I, the newborn rectal temperatures and the total used dose of ephedrine were significantly higher than Group B ($p < 0.05$). The amount of ephedrine used in the baby's birth before and after the Group I higher than Group B ($p < 0.05$) (Table II). There were no significant differences in the prevalence of shivering or thermal comfort scores at any time observed between the groups (Table III).

In Group I, the systolic and mean arterial blood pressures which were measured at the 9, 12 and 18th minutes were higher than Group B ($p < 0.05$). There were no differences between two groups concerning the adverse effects such as nausea, vomiting, pain.

There were no difference in neonatal outcome as measured by Apgar scores at the 1st and 5th minutes after delivery, and umbilical blood gas values (Table IV).

Discussion

In the present study, we observed that the core temperatures of mother and newborn were higher, and the regulation of blood pressure was better with the administration of ephedrine bolus and infusion with a infusion pump when compared with bolus ephedrine to prevent maternal hypotension after the spinal anaesthesia.

Warming of the local anaesthetic solutions, age, sensory block level, and operating room temperature may affect the development of hypothermia during the operation[12]. The operation room temperature was set at 22°C. The temperature and amount of fluids were set in the same way. On entering the operative room (OR), patients were covered with one cotton blankets by the OR nurse. The level of the sensorial blockade was similar in all patients.

Intraoperative core hypothermia during neuraxial anaesthesia occurs because of a number of

Table II. Anaesthetic details. Values are mean ± SD, median (range), percentage or number.

	Group I (n = 55)	Group B (n = 55)	*p* value
Intra-op. fluid (ml)	1227.2 ± 221.4	1158.1 ± 150.2	0.060
Sensory block level	T4 (T8-T4)	T4 (T8-T4)	0.084
Ephedrine (mg)	34.03 ± 11.5*	21.7 ± 11.8	0.001
Ephedrine before the birth of baby (mg)	20.01 ± 10.1*	10.8 ± 9.8	0.002
Time of hypotension (min)	5 (2-15)	5 (2-16)	0.075
Hypotension before the birth of baby (%)	24%	49%	0.039
Hypothermia before the birth of baby (n)	18/55*	23/55	0.003
Hypothermia after the birth of baby (n)	18/55*	24/55	0.003

*$p < 0.05$ Group I versus Group B

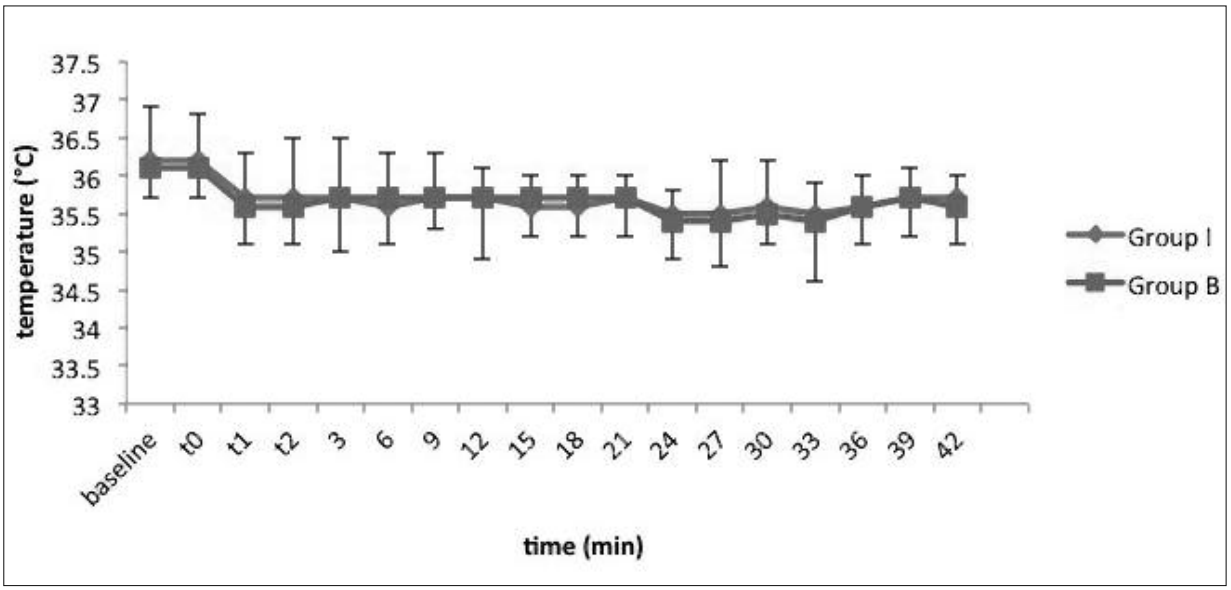

Figure 2. Change in peripheral temperature with time.

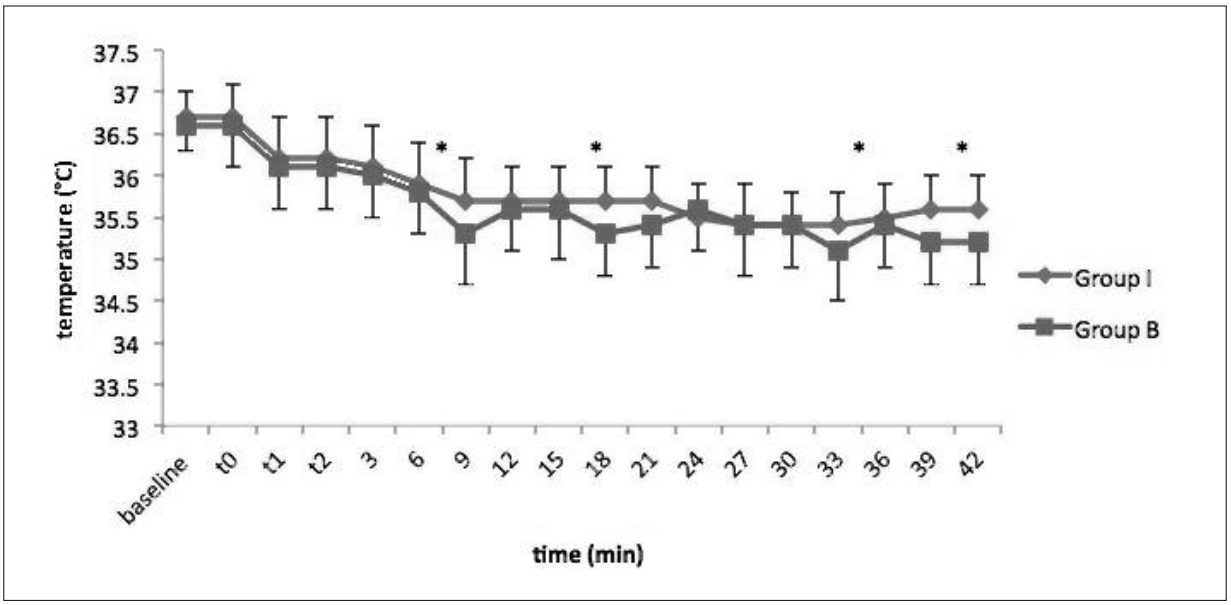

Figure 3. Change in core temperature with time,

Table III. Intra-operative thermal comfort score and shivering of groups. Values are mean ± SD or percentage (%) or number.

	Group I (n = 55)	Group B (n = 55)	*p* value
Thermal comfort			
4	17 (30.9 %)	14 (25.4%)	0.086
5	35 (63.6 %)	32 (58.1%)	0.073
6	3 (5.4%)	3 (5.4%)	1.000
Shivering; n	5	3	0.092
No shivering; n	50	52	0.089

Table IV. Newborn outcomes. Values are mean ± SD or median (range).

	Group I (n = 55)	Group B (n = 55)	*p* value
The warmest temperature of the infant; °C	37.6 ± 1.2	37.7 ± 1.1	0.093
Rectal temperature; °C	36.6 ± 0.4*	36.4 ± 0.3	0.048
Apgar, 1st min.	8 (5-10)	8 (6-10)	0.099
Apgar, 5th min.	9 (7-10)	9 (7-10)	1.000
pH venous blood	7.35 ± 0.08	7.36 ± 0.07	0.864
pH arterial blood	7.33 ± 0.07	7.33 ± 0.06	0.899

*$p < 0.05$ Group I versus Group B.

processes that impair thermoregulation. Core-to-peripheral redistribution heat by vasodilation is the major cause of core hypothermia in the first hour of neuraxial anaesthesia. Neuraxial anaesthesia[13] also reduces thermoregulatory vasoconstriction and shivering thresholds by approximately 0.5°C. Accordingly, there may have been an influence of vasoconstriction caused by ephedrine on heat distribution in our patients. Also ephedrine mediates its thermogenic effects primarly by enhancing the sympathetic neuronal release of norepinephrine and epinephrine, which stimulates directly brown adipocyte respiration via the beta-adrenoreceptors[10]. Ephedrine crosses the human placenta and may stimulate alteration of fetal metabolism[14].

Ephedrine has slow onset of action making it difficult to titrate an appropriate bolus dose[14]. Tachyphylaxis occurs with ephedrine so repeated doses may become ineffective[14,15]. This factor was demonstrated by Persky et al[15]. The mechanism for this may involve reduction in receptor number, counter regulation, depletion of neurotransmitter pool or receptor desensitization. For this reason, ephedrine infusion group was included in this study. Altough the lack of correlation between blood pressure and body temperature, the amount of ephedrine that regulate the hemodynamia was higher in infusion group (12.33 mg higher than bolus alone group at the end of surgery). Therefore, thermogenic properties of ephedrine was observed in our work.

Fallis et al[16] have reported that mild maternal hypothermia associated with neuraxial anaesthesia precipitates hypothermia in the newborn. Concomitant effects of newborn hypothermia may be seen in the physical and metabolic status of the infant at birth and immediate postbirth period. Fetal temperature is, thus, directly related to maternal temperature is likely to be associated with hypothermia in newborn infants[3]. To prevent maternal hypothermia actively heated blankets[16] or warm fluid were used[17]. However, all of these techniques are expensive and require time[16,17]. Moreover, these techniques do not treat hypotension.

Woolnough et al[17] have showed that, warming intravenous fluids mitigates the decrease in maternal temperature during elective caesarean section under combined spinal-epidural anaesthesia and improves thermal comfort, but does not affect shivering. In that study, the ambient theatre temperature was 24°C and the temperature of intravenous fluids that was given to the patient was 40-41°C. Whereas, the ambient theatre temperature was 22°C, and all the intravenous fluids were given at room temperature in our study. We found that the application of ephedrine either bolus or infusion reduced the occurrence of shivering, unlike the results of Woolnough et al[17]. The mechanism of ephedrine application on the redistribution of core temperature with vasoconstrictor effect may affect this difference in our study.

Yokoyama et al[18] demonstrated that when they administered warmed colloid solution followed by warmed crystalloid solution to elective cesarean patients, they prevented the development of hypothermia in mothers. In addition, they found that the administered warmed solution increases the Apgar score at first minute, and a higher rate of normal umbilical arterial pH than the neonates in the control group. As the authors point out, this anaesthetic technique was similar to the technique we have used in our study. However, they did not report the difference of rectal temperatures at birth. On the contrary, in our experience in the ephedrine infusion administered group the rectal temperatures at birth were higher than their measurement. The difference in the warming modality techniques might explain this dissimilarity.

In a study by Horn et al[3] epidural anaesthesia was induced after 15 minutes of prewarming with a forced-air blanket. Warmed IV fluids were

given both to the study and control groups. They found that neonates in the study group had a higher umbilical vein pH and higher rectal temperatures at birth. Apgar scores, however, were similar. Of note, they have found that there was less shivering in mothers in the study group. They had epidural anaesthesia as a technique different from ours. According to that research, higher core temperature continued for two hours. In our study, Apgar scores and umbilical vein pH were similar for the each group.

Butwick et al[13] were unable to show any statistically significant difference in maternal core temperature, frequency of shivering, umbilical cord pH, or neonatal Apgar scores in a small group of elective caesarean section patients who were warmed using intraoperative lower body forced-air devices in mothers receiving spinal anaesthesia.

However, there is no available phenylephrine IV form in our country. Due to this reason, we have to use ephedrine. As low dose of ephedrine (< 30 mg) was used in our work no significant difference in Apgar scores and umbilical vein pH were observed. Investigations showed that high dose of ephedrine may cause neonatal acidosis[19,20]. Although the reports demonstrating adverse fetal acid-base outcomes are compelling, there is no evidence that ephedrine use results in adverse neonatal outcome in normal, healty pregnancies. The use of ephedrine in the compromized fetus may be more clinically significant[14]. Umbilical cord blood samples was in physiologic range as all babies were healty in our research. The reason for the low score of shivering was attributed to preventive properties of redistribution and thermogenic effect[21] of ephedrine. Also we thought that the bolus dose of ephedrine prevented shivering. There was no difference in the prevalence of nausea or vomiting between bolus and infusion groups. This might be explained with the time of the hypotension that was similar between two groups.

Ethically we were unable to create a control group which was not using ephedrine.

Conclusions

As a result, we found that combined bolus and infusion of ephedrine for treating maternal hypotension in patients who underwent Caesarean section under spinal anaesthesia, prevent maternal and neonatal hypothermia. We think that these two effects of this drug might be beneficial for clinical practice.

Conflict of Interest

None declared.

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