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Effect of hypertonic sodium chloride hydroxyethyl starch 40 on ET, TXB2, 6-keto-PGF1α, and ANP of preeclampsia in caesarean section

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Summary

Objective: Preeclampsia is a unique disease of pregnancy. Delivery via caesarean section is the most important way of terminating the pregnancy and treating preeclampsia. Perioperative fluid therapy is performed to maintain the circulatory volume and reduce tissue edema. This study evaluated the effects of hypertonic sodium chloride hydroxyethyl starch 40 (HSH40) as perioperative fluid therapy for preeclampsia patients. *Materials and Methods:* Forty preeclamptic women were randomly divided into two groups: the Ringer's solution group and the HSH40 group. Their ECG, HR, MAP, and SPO_2 were monitored. Their MVP and HR were recorded at five, eight, and ten minutes after anesthesia induction and at the end of the caesarean section. The corresponding volume of infusion, blood loss, and urine output during the operation were also recorded. Venous samples were collected before HSH40 infusion and 30 min after infusion to measure the plasma concentrations of ET, TXB_2, 6-keto-$PGF_{1\alpha}$, and ANP via a radioimmunoassay. *Results:* HSH40 infusion significantly decreased the plasma ET levels ($p < 0.01$), significantly changed the plasma ANP and TXB_2 levels ($p < 0.05$), and significantly increased the plasma 6-keto-PGF1α levels ($p < 0.01$) in the experimental group compared with those before infusion. The plasma levels of ET, ANP, TXB_2, and 6-keto-PGF1α did not significantly change in the control group. Compared with T1, MAP decreased significantly at T2, T3, T4, and T5 within groups ($p < 0.05$) and between the two groups. MAP significantly changed at T2, T3, T4, and T5 ($p < 0.05$). HR did not significant change at T1, T2, T3, T4, and T5 within or between groups. Volume of infusion and urine volume significantly differed between groups ($p < 0.05$). *Conclusion:* Low-dose HSH40 lowers the plasma levels of vasoconstrictor substances (ET and TXB_2) and increases the levels of vasodilator substances (6-keto-PGF1α and ANP) during preeclampsia. It effectively maintains and stabilizes the circulating blood volume, increasing renal blood flow, which improves renal function and increases urine output.

Key words: Hypertonic sodium chloride hydroxyethyl starch; Preeclampsia; Endothelin; Atrial natriuretic peptide; Prostacyclin.

Introduction

Preeclampsia is a pregnancy-specific disease and a serious stage of hypertensive disorder during pregnancy. Preeclampsia is the main cause of maternal and perinatal morbidity and mortality. The basic pathophysiology includes systemic small artery spasm. The vascular spasms significantly increases plasmic endothelin (ET) in patients with hypertensive disorders during pregnancy than in normal pregnant women and is positively correlated with the severity of the disease [1-3]. Elevated ET prompts a massive release of atrial natriuretic peptide (ANP), which is significantly higher than that during normal pregnancy [4]. Vasospasms significantly reduce plasma prostacyclin (PGI_2) and significantly increase thromboxane (TXB_2), further aggravating the vasoconstriction, elevating blood pressure, and causing further coagulation disorders. The imbalance of these four vasomotor substances is the main cause of pregnancy-induced hypertension and an important reason for the maternal systemic spasms in small arteries, low blood volume and concentration, viscosity-induced maternal hypoperfusion of vital organs, tissue ischemia, hypoxia, acidosis, blood stasis, decreased deformation force of erythrocytes, significantly increases platelet aggregation, and a series of pathophysiologic changes [5]. Timely termination of pregnancy is the effective treatment for preeclampsia. The main way for terminating pregnancy is delivery via caesarean section. The type and dose of infusion during maternal preeclampsia caesarean section remain controversial. Hypertonic saline hydroxyethyl starch (HSH) is a hypertonic colloidal volume expander that actively expands the blood volume, stabilizes and maintains the effective circulating blood volume, improves the microcirculation, improves the tissue oxygen supply, reduces tissue edema, corrects acidosis, reduces blood viscosity, and exerts a diuretic effect. Hypertonic sodium chloride solution (hyperosmotic saline, HS) changes the levels of hormones and cytokines [6, 7]. Expanding the blood volume increases the cardiac filling pressure and significantly increases the effective plasma ANP levels, increases intracellular Ca^{2+}, activates enzymes re-

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quired for synthesis, and directly stimulates endothelial cells to elevate plasma PGI_2 synthesis. HS also produces an endogenous infusion effect, improves microcirculation, promotes ANP release, influences lysosomal function, and inhibits the secretion of ET [8]. In this study, puerperants with maternal preeclampsia underwent waist-epidural anesthesia for caesarean section and were then injected with HSH. After preeclampsia, the plasma ET, TXB_2, PGI_2, and ANP levels, and the basic vital signs of the mothers and their infants were taken. The present authors further explored the possible mechanism of action of the intraoperative transfusion of small doses of HSH for preeclampsia.

Materials and Methods

Subjects

Severely preeclamptic patients who were admitted into the present unit from May 2007 to July 2008 were enrolled into the case cohort. According to the criteria of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [9], preeclampsia is defined as systolic blood pressure (SBP) >140 mmHg, diastolic blood pressure (DBP) >90 mmHg, or both, and proteinuria >100 mg/dl. Patients in labor, those with chronic hypertension, placental abruption, diabetes, or coagulopathy, and those given β-tocolytic drugs were excluded from the study. This study was conducted in accordance with the Declaration of Helsinki and with the approval from the Ethics Committee of the Third Hospital of Zhengzhou University. Written informed consent was obtained from all participants.

Grouping

The patients who provided their written informed consent to participate in this study were randomly assigned using a random number table for block randomization via numbered sealed envelopes. The groups received either Ringer's solution (RS group of 20) or HSH solution (HHS group of 20). In the operating room, all patients were monitored with standard monitoring devices, including an automated blood pressure cuff, an electrocardiogram, and pulse oximetry.

Before administering combined spinal-epidural anesthesia, five ml/kg of HHS consisting of 4.2% hypertonic saline and 7.2% hydroxyethyl starch was infused for over 20 minutes, followed by Ringer's solution at 100 ml/h. The RS group received continuous Ringer's solution (0.9% sodium chloride, nine g/l sodium chloride, osmolarity 309 mOsmol/l, Na^+ concentration 154 mmol/l).

Combined spinal-epidural anesthesia was induced in all cases in the lateral decubitus position, at L2-L3 or L3-L4, with 1.5 ml of 0.75% hyperbaric bupivacaine via a 22-gauge spinal needle injected for 20 seconds under aseptic conditions by an anesthesiologist who was blinded to the study groups. The spinal needle was removed and an epidural catheter was inserted three to four cm into the epidural space and was secured with tape. The parturient was then immediately placed in the supine position with left uterine displacement. The patient reaching a sensory level of T8 was determined bilaterally at 15 minutes using pinprick (patients who were induced higher than T6, but lower than T10 were excluded from the study). The plasma concentrations of ET, TXB_2, 6-keto-PGF1α, and ANP were measured from blood collected via a peripheral vein before HSH infusion and at the end of surgery. The blood samples were transferred into chilled disposable tubes containing aprotinin (1,000 kallikrein inactivator units/ml) and EDTA (one mg/ml) and immediately centrifuged at 4°C. The plasma aliquots were stored at -70°C for the assay. Mean arterial blood pressure (MAP) was measured every minute for the first 20 minutes, every two minutes for the next ten minutes, and every five minutes thereafter until the end of the surgery. Heart rate (HR) was noted via continuous electrocardiography. The volume of infusion, urine output, and blood loss during the operation, as well as newborn weight, Apgar scores, and neonatal intensive care unit admission were recorded by the anesthetist.

Determination of plasma ET levels

ET levels were determined using a Parameter Human ET enzyme-linked immunosorbent assay kit . ET was isolated from one ml of plasma in 1.5 ml of extraction solvent (40:1:5, acetone: 1 N HCl: water). The extraction procedure was performed according to the protocol outlined in the sample preparation of the manufacturer's instructions. The assay displayed a sensitivity of 1.0 pg/ml, and inter-assay and intra-assay variability of 10%.

Determination of plasma ANP levels

The plasma ANP concentration was measured by radioimmunoassay as previously described. This radioimmunoassay recognizes a carboxy-terminal fragment of ANP; the minimal detectable quantity of ANP is one pg/tube. The 50% binding intercept of the standard curve was 20 pg/tube. Intra-assay and inter-assay variances were 7.0% and 12.3%, respectively.

Determination of plasma TXB_2 and 6-keto-PGF1α levels

The authors took 6-keto-prostaglandin Flα (6-keto-PGFla) and TXB_2 as indices of plasma PGI_2 and TXA_2 levels, the indices used for the systemic level of PGI_2 and TXA_2. TXB_2 was determined using a competitive enzyme-linked immunosorbent assay of stable analog TXB_2 (16). The concentration of immunoreactive 6-keto PGFlα was determined in non-extracted samples of PBS incubated with isolated rabbit cerebral microvessels. The radioimmunoassay procedure was performed as detailed. The detection limit of the 6-keto PGFlα antisera was ten pg/tube, and intra-assay and inter-assay variation was routinely less than 10%.

Statistical analysis

Data are presented as numbers, medians, and ranges, means ± SD, or percentages, as appropriate. An unpaired Student's t-test was used for normally distributed data, whereas a Mann-Whitney U test was used for non-normally distributed data. Kruskal-Wallis and Dunn tests were used to analyze the time course of mean BP and HR. Paired Student's t-test was used to compare these variables between before and after transfusion. Differences with p values < 0.05 were considered statistically significant.

Results

Demographic characteristics

The demographic characteristics of the two study groups are shown in Table 1. The groups did not significantly differ in terms of maternal age, weight, and parity or gestational weeks. The blocks were generally accomplished on the first attempt. A similar number of dermatomal segments (assessed by pinprick) were blocked in both groups.

Biochemical analyses

HSH infusion at five ml/kg into the preeclamptic patients significantly changed their ET, TXB2, 6-keto-PGF1α, and ANP levels relative to those of the control group (Table 2).

Table 1. — *Demographic characteristics of the two patient groups.*

Variable	Experimental group	Control group
Age (yrs)	30.05±3.48	29.85±3.10
Weight (kg)	79.95±7.56	78.90±7.83
Gestational weeks (w)	35.00±2.29	35.35±2.18
Skin incision to skin closure interval (min.)	23.65±4.42	22.84±4.28

Data are mean ±SD.

Table 2. — *Effect of HSH on plasma ET, TXB2, 6-Keto-PGF1α, and ANP changes in preeclamptic patients.*

	Group	Pre-transfusion	Post-transfusion
ET	Experimental group	91.73±18.57	81.61±11.12▲
	Control group	92.45±18.89	90.91±16.92
ANP	Experimental group	208.03±59.12	229.40±50.71▲
	Control group	209.97±52.66	206.72±51.08
TXB_2	Experimental group	275.80±46.41	244.77±49.21▲
	Control group	273.29±43.21	268.56±45.04
6-Keto-$PGF_{1\alpha}$	Experimental group	81.01±12.74	104.86±16.56▲
	Control group	83.84±15.65	87.62±14.53

Data are mean ± SD.
Before administering combined spinal-epidural anesthesia, HSH was given to preeclamptic patients over 20 minutes in experimental group, control group received Ringer's solution. ▲$p < 0.05$ or $p < 0.01$.

The levels of plasma ET, ANP, TXB_2, and 6-keto-PGF1α were not significantly changed in the control group. Compared with those before HSH infusion, the levels of plasma ET and TXB2 decreased significantly, whereas plasma 6-keto-PGF1α and ANP increased significantly.

Hemodynamic parameters and volume input and output data

The MAP and HR values of both groups are shown in Table 3. As illustrated in Table 3, both groups had similar MAP values measured during the preoperative period. The MAP measured during the induction until the delivery period was consistently lower in the control group than in the experimental group (Table 3). The control and experimental groups did not significantly differ in the duration of anesthesia. The volume of infusion in the experimental group was less than that of the control group, whereas the urine volume of preeclamptic patients was higher than that of the control group (Table 4). The volume of blood loss did not significantly differ between groups (Table 4). The two groups had similar newborn weights, Apgar scores, and admission rates into the neonatal intensive care unit.

Table 4. — *Volume in- and output.*

	Volume of infusion (ml)	Volume of blood lose (ml)	Urine volume (ml)
Experimental group	737±95*	195±36	252±59*
Control group	860±109	190±32	192±40

Data are mean ± SD, Unpaired Student's t-test, *$p < 0.05$.

Discussion

Preeclampsia is a unique disease of pregnancy. Caesarean section is the most important way of terminating pregnancy and treating preeclampsia. Perioperative fluid therapy needs to maintain the circulatory volume and reduce tissue edema. Ringer's solution temporarily increases blood volume, and its massive infusion leads to tissue edema. A small volume of HSH40 produces more rapid volume expansion, increases cardiac output, systemic blood pressure, and microvascular perfusion, and it reduces tissue edema [10-13].

In this study, the levels of plasma ET decreased significantly compared with those before HSH infusion (Table 2). Thus, HSH may have inhibited angiotensin II (Ang II), which stimulates ET secretion from cultured bovine endothelial cells via a receptor-mediated process [14-16]. Moreover, HSH may have enhanced ANP secretion, which interacts with ET secretion from the endothelium through the renin–angiotensin system [17, 18]. Compared with Ringer-Locke liquor, HSH40, which inhibits ET secretion, may improve the symptoms of preeclampsia.

As already mentioned, 6-keto- PGFlα and TXB_2 mainly reflect the plasma levels of PGI_2 and TXA_2. The 6-keto-PGFlα levels in the experimental group were significantly increased compared with that before HSH infusion, whereas TXB_2 was significantly reduced (Table 2). The levels of both TXB_2 and 6-keto-PGFla did not significantly change in the control group.

Colloidal liquid of HSH40 maintains the effective circulating blood volume. Furthermore, the hypertonic saline in HSH40 potentiates ANP secretion [19] and strongly inhibits

Table 3. — *Hemodynamic data in the both groups.*

	Group	Pre-transfusion (T1)	Post-transfusion 5 min (T2)	Post-transfusion 8 min (T3)	Post-transfusion 10 min (T4)	End (T5)
MAP (mmHg)	Experimental group	127.2±7.9	102.9±14.2▼#	85.8±10.2▼#	106.7±7.6▼#	107±14.5▼#
	Control group	127.3±8.2	91.4±10.6▼	74.3±8.5▼	93.5±8.2▼	96.1±11.7▼
HR (bpm)	Experimental group	102.2±13.3	103±11.4	96.4±8.1	98.6±8.6	98.3±8.2
	Control group	101.7±14.2	103.4±11.8	98.2±9.6	99.7±8.4	98.5±10.4

Data are mean ± SD, Unpaired Student's t-test, ▼$p < 0.05$; Paired Student's t-test, # $p < 0.05$.

immunoreactive ET secretion in the aorta. Therefore, increased circulating ANP may affect ET secretion. The diuretic mechanism of HSH40 may involve the instantaneous mobilization of extravascular fluid into the intravascular space through the osmotic action of HSH40 [20, 21] and its subsequent rapid excretion via the action of extracellular fluid expansion and by the action of ANP. Furthermore, hypertonic saline solution may facilitate the action of ANP and help overcome an established ANP resistance, as demonstrated by increased renal blood flow. In fact, HSH administration potentiates the diuretic action of ANP and possibly helps overcome ANP resistance without requiring a higher concentration, thereby minimizing electrolyte disturbances and other side effects (e.g., hypotension).

In summary, low-dose HSH40 lower the levels of vasoconstrictor substances (ET and TXB2) and increases the levels of vasodilator substances (6-keto-PGF1α and ANP) in preeclampsia. HSH40 effectively maintains and stabilizes the circulating blood volume, increasing the renal blood flow, which improves renal function and increases the urine output.

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