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Safety and beneficial effect on body core temperature of a prewarmed plasma substitute—hydroxyethyl starch—during anesthesia

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Abstract
Purpose. We investigated, first, the safety of use and stability of a plasma substitute—hydroxyethyl starch (HES)—kept in a warming cabinet for a long period, and then the effect on body core temperature of the prewarmed HES in patients during urological surgery.
Methods. In the first part of the study, HES colloid solutions (500 ml per pack; Hespander) were kept in a warming cabinet (40°C) for 3 months and were tested for biological and chemical safety and stability. In the second part of the study, 1000 ml of HES at room temperature (control group; $n = 10$) or kept in a warming cabinet for a few days (warmed group; $n = 10$) was infused via a central venous catheter for 30 min in patients undergoing urological surgery under general anesthesia with lumbar epidural anesthesia. Esophageal temperature was monitored as the core temperature. HES fluid temperatures in the pack and at the end of a 1-m intravenous tube connected to the central venous catheter were also measured.
Results. The test of HES products warmed for 3 months passed all inspections performed during the study period. In the warmed group, the pack and intravenous tube temperatures of HES were still high at 15 min after infusion (37.1° ± 1.5°C [mean ± SD] and 34.8° ± 2.2°C, respectively). Core temperature in the warmed group decreased significantly, by 0.34° ± 0.06°C, but was significantly higher than that in the control group (by 0.84° ± 0.13°C) after 30 min of the infusion.
Conclusions. The use of HES products kept in a warming cabinet prior to surgery can maintain warm body temperature, easily, safely, and effectively.

Key words Hydroxyethyl starch (HES) · Warming cabinet · Core temperature · Infusion rate · Intravenous tube

Introduction

It is well established that mild hypothermia increases not only blood loss and transfusion requirements [1] but also increases the incidence of morbid cardiac events [2] and surgical-wound infection [3], leading to prolongation of hospitalization [3]. It is also known that rapid intravenous infusion of crystalloid solution can cause mild hypothermia, depending on the fluid temperature [4,5] and route of intravenous administration [5]. Plasma substitutes such as hydroxyethyl starch (HES) are often administered rapidly to patients with hypovolemia [6] and for hemodilutional autotransfusion (HAT) [7] during surgery and anesthesia. Colloid solutions such as HES appear to have stronger effects on body core temperature than crystalloid solutions, because colloid solutions remain almost entirely in the intravascular space and flow into the heart directly [8]. Accordingly, prewarmed HES can be expected to maintain body core temperature, easily, safely, and effectively.

In this study, we investigated, first, the safety of use and stability of HES kept in a warming cabinet under conditions of 40°C and 75% relative humidity for 3 months. We then investigated the beneficial effect on body core temperature of prewarmed HES in patients during urological surgery.

Subjects, materials, and methods

Safety and stability of HES kept in a warming cabinet

Three packs of HES colloid solution (Hespander; 500 ml in a plastic pack; Kyorin Pharmaceutical, Tokyo, Japan) were randomly selected and kept in a warming cabinet (OP-7020W; Central Uni, Kitakyushu, Japan) at approximately 40°C and 75% relative humidity for 3 months, in order to test the safety and stability of the solution. The solution contained (in $g \cdot 100\,ml^{-1}$) 6.0 g hydroxyethyl starch (mean molecular weight, 70000, substitution rate for hydroxyethyl base, 0.55), 0.5 NaCl, 0.03 KCl, 0.02 $CaCl_2$, 0.224 lactate sodium, and 1.0

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glucose. The tests performed were as follows: (1) tests of characteristics (appearance, viscosity, and osmotic pressure); (2) recognition tests (1–9); (3) pH test; (4) purity tests (heavy metals and arsenic); (5) intrinsic viscosity test; (6) antigen test; (7) insoluble substances test; (8) aseptic test; and (9) quantitative tests for HES and glucose. The recognition tests were: 1 to 3, HES reactions to anthrone solution, iodine solution, and ethanol; 4, glucose reaction to Fehling's solution; 5 to 7, qualitative reactions to potassium, calcium, and sodium salts; 8, qualitative reaction to chloride substances; and 9, λ max, as determined by ultraviolet spectrum (wavelength of 337–343 nm for disodium lactate). We tested all of these items at the beginning of the study, and after 1-month, 2-month, and 3-month storage of the HES in a warming cabinet. Although detailed explanations of the methods used are omitted, evaluation criteria are listed in Table 1.

Effect on body core temperature of prewarmed HES during anesthesia

This study was approved by our institutional Ethics Committee on Human Research, and informed consent was obtained from each patient. We studied 20 American Society of Anesthesiologists (ASA) physical status I or II adult patients who required general anesthesia with lumbar epidural anesthesia for urological surgery (e.g., radical prostatectomy and total cystectomy). The subjects were all appropriate for HAT by virtue of having sufficient concentrations of hemoglobin ($>13.0\,mg\cdot dl^{-1}$). Patients with a history of thyroid disease, dysautonomia, Raynaud's syndrome, or malignant hyperthermia were excluded from the study. The patients were premedicated with an intravenous administration of midazolam ($0.05\,mg\cdot kg^{-1}$) 30 min before the operation. No other premedication was given.

Studies began at approximately 8:15 a.m., and all patients fasted for 8 h before the study. An intravenous catheter was inserted into an antecubital vein in the left arm, and acetated Ringer's solution at room temperature was infused at approximately $10\,ml\cdot kg^{-1}\cdot h^{-1}$, and a tracheal tube was introduced. Anesthesia was maintained with 0.8%–1.0% sevoflurane and 66% nitrous oxide in oxygen during the study. After the insertion of another intravenous catheter into a cubital vein in the right arm, 800–1200 ml of venous blood was drawn from the catheter for HAT for approximately 20 min. Ephedrine at doses of 5 mg, was injected repeatedly, up to a total of 40 mg, to maintain arterial blood pressure at ±20% of basal value.

The patients were randomly allocated, by an envelope technique, to one of two groups to receive HES kept at room temperature (control group; $n = 10$) or HES kept in a warming cabinet (warmed group; $n = 10$). The temperature of the warming cabinet was kept at approximately 40°C. Just after the withdrawal of autologous blood, 1000 ml of HES at room temperature or kept in a warming cabinet for a few days was infused via a central venous catheter (inserted before the study began) for approximately 30 min. During the study, esophageal temperature was monitored continuously as the core temperature (CTM-303; Terumo, Tokyo, Japan). The HES fluid temperatures in the pack and at the end of a 1-m tube connected to the central venous catheter were measured with thermocouples (Luer lock sensor; Mallinckrodt Japan, Tokyo, Japan) and with a temperature monitor (Mon-a-Therm model 6510; Mallinckrodt Japan). Ambient temperature and relative humidity were set at 22°C and 40%, respectively. No warming systems were used during the study; however, when the esophageal temperature of the patients fell below 35.0°C, a forced-air warming system (Bair Hugger; Augustine Medical, Eden Prairie, MN, USA) was used to warm the patients, and these patients were excluded from the study. All of the parameters were measured before the surgical incision.

Values were expressed as means ± SD. Power analysis ($\alpha = 0.01$, $\beta = 0.1$) provided an appropriate sample size of 10–12. Measured temperatures are shown as absolute values or relative changes (0°C at the beginning of the study). Differences in demographic data between the groups were analyzed using the two-tailed *t*-test. Changes in esophageal and HES temperatures were analyzed using one-way analysis of variance (ANOVA) for repeated measurements, and Fisher's test was used as a post hoc test. In all comparisons, $P < 0.05$ was considered significant.

Results

Safety and stability of HES in a warming cabinet

Table 1 shows the results obtained for the safety and stability of HES kept in a warming cabinet for 3 months under conditions of 40°C and 75% relative humidity. The test of HES products warmed for 3 months passed all inspections conducted during the study period.

Effect on body core temperature of prewarmed HES during anesthesia

Ten patients were studied in each group, and all patients completed the study without severe complications. Demographic characteristics, esophageal temperature at the beginning of the study, duration of surgery, duration of anesthesia, volume of HAT, and volume of blood loss are presented in Table 2. None of these parameters differed between the groups. Changes in HES

Table 1. Results for safety and stability of hydroxyethyl starch (plastic pack, 500 ml) stored under conditions of 40°C and 75% relative humidity for 3 months

	Items of inspection	Evaluation criteria	Lot no.	At the beginning of the test	1 Month	2 Months	3 Months
Tests of characteristics	Appearance	Colorless, clear liquid	I	Yes	Yes	Yes	Yes
			II	Yes	Yes	Yes	Yes
			III	Yes	Yes	Yes	Yes
	Viscosity	Slight	I	Slight	Slight	Slight	Slight
			II	Slight	Slight	Slight	Slight
			III	Slight	Slight	Slight	Slight
	Osmotic pressure ratio	0.8–1.2	I	1.1	1.1	1.1	1.1
			II	1.1	1.1	1.1	1.1
			III	1.1	1.1	1.1	1.1
Recognition tests[a]		(1) to (9)	I	Passed	Passed	Passed	Passed
			II	Passed	Passed	Passed	Passed
			III	Passed	Passed	Passed	Passed
pH test		5.0–7.0	I	5.8	5.6	5.4	5.3
			II	5.7	5.4	5.3	5.2
			III	5.6	5.4	5.3	5.2
Purity tests	Heavy metals	≤1 ppm	I	≤1 ppm	≤1 ppm	≤1 ppm	1 ppm
			II	≤1 ppm	≤1 ppm	≤1 ppm	1 ppm
			III	≤1 ppm	≤1 ppm	≤1 ppm	1 ppm
	Arsenic	≤0.1 ppm	I	≤0.1 ppm	≤0.1 ppm	≤0.1 ppm	0.1 ppm
			II	≤0.1 ppm	≤0.1 ppm	≤0.1 ppm	0.1 ppm
			III	≤0.1 ppm	≤0.1 ppm	≤0.1 ppm	0.1 ppm
Intrinsic viscosity test		0.09–0.14	I	0.12	0.12	0.12	0.12
			II	0.12	0.12	0.12	0.12
			III	0.12	0.13	0.12	0.12
Antigen test		Experimental animals not exhibiting dyspnea, collapse, or death at 30 min and 24 h after injection	I	Passed	Passed	Passed	Passed
			II	Passed	Passed	Passed	Passed
			III	Passed	Passed	Passed	Passed
Insoluble substances test		≤2·ml^{-1}	I	0.0	0.0	0.0	0.0
			II	0.0	0.1	0.1	0.0
			III	0.0	0.0	0.1	0.0
Aseptic test		None	I	Passed	Passed	Passed	Passed
			II	Passed	Passed	Passed	Passed
			III	Passed	Passed	Passed	Passed
Quantitative tests	HES	5.7%–6.3% (w/v)	I	5.9	6.1	6.1	5.9
			II	5.9	6.2	6.2	6.0
			III	5.9	6.0	6.2	6.0
	Glucose	0.90%–1.10% (w/v)	I	0.97	1.01	1.01	1.00
			II	1.00	1.02	1.01	0.99
			III	0.98	1.00	1.00	0.99

HES, hydroxyethyl starch

[a] Recognition (1)–(9): 1, HES reaction to anthrone solution; 2, HES reaction to iodine solution; 3, HES reaction to ethanol; 4, glucose reaction to Fehling's solution; 5–7, qualitative reactions to potassium, calcium, and sodium salts; 8, qualitative reaction to chloride substances, and 9, λ max, as determined by ultraviolet spectrum (wavelength of 337–343 nm for disodium lactate)

Table 2. Patients' characteristics, esophageal temperature at the beginning of the study, duration of anesthesia, duration of surgery, volume of HAT, and volume of blood loss

Variable	Control group ($n = 10$)	Warmed group ($n = 10$)
Age (years)	65 ± 8	68 ± 7
Weight (kg)	62 ± 6	63 ± 8
Height (cm)	161 ± 12	163 ± 11
Sex (female/male)	2:8	1:9
Esophageal temperature at the beginning of the study (°C)	36.8 ± 0.3	36.7 ± 0.4
Duration of surgery (min)	420 ± 123	400 ± 101
Duration of anesthesia (min)	503 ± 131	512 ± 114
Volume of HAT (g)	1013 ± 132	1054 ± 103
Volume of blood loss (g)	1254 ± 342	1342 ± 412

Values are means ± SD
HAT, hemodilutional autotransfusion

fluid temperatures in one pack of 500 ml and at the end of the intravenous tubing for the first 15 min are shown in Fig. 1. The pack and intravenous tubing temperatures of HES that had been kept at room temperature exhibited no significant changes and remained at about 21°C–22°C during the study (Fig. 1; closed squares). In contrast, both the pack and intravenous tubing temperatures of HES prewarmed in the cabinet exhibited small but significant decreases during the study; however, both temperatures were still high at 15 min after infusion (37.1° ± 1.5°C and 34.8° ± 2.2°C, respectively) (Fig. 1; closed circles). Figure 2 shows relative changes in esophageal temperature during the study period. In the control group, in which HES at room temperature was infused centrally and rapidly, the core temperature decreased significantly, by approximately 0.80°C, during the infusion and remained at this level 30 min after infusion. In the warmed group, in which HES was prewarmed to temperatures of up to 40°C, the core temperature decreased significantly, by approximately 0.30°C, but it was significantly higher than that in the control group ($P < 0.05$). After the 60-min period of the study, all patients were actively warmed using an electric blanket, warmed intravenous solution, and/or a forced-air warming system. The esophageal temperatures in both groups gradually increased during the surgery and were within ±0.2°C of the preoperative values at the end of surgery, and there were no significant differences in temperature between the groups.

Discussion

Our in vitro study revealed that HES in packs including glucose can be kept safely and stably in a warm environment of up to 40°C for 3 months. Because plasma substitutes such as HES are commonly used during surgery and anesthesia, one or two packs of HES (500–1000 ml) can be routinely kept in a warming cabinet in each operating room.

Our in vivo study revealed that prewarmed HES partially but significantly prevented the decrease in core temperature observed in the control group (Fig. 2). There are some reports that warmed intravenous fluid infusion can maintain body core temperature adequately [4,9,10]. The simplest method is to keep intravenous fluids warm before administration. Although a few scientific papers have appeared referring to the use of a microwave heater for intravenous fluids [11,12], it has already been pointed out that microwave heating could induce overwarming [13,14]. Warming cabinets are widely employed to keep intravenous fluids warm in the operating room prior to use [15]. The main disadvantage of this technique is a substantial decrease in fluid temperature during administration, depending on the thickness of the intravenous tubing used [16], its length [15,17,18], and the rate of flow of the intravenous fluid [15,17,18]. It would be meaningless to use the prewarmed intravenous fluids in children [15], because the intravenous tubing is thin and the rate of flow of intravenous fluid is low.

Plasma substitutes such as HES are usually administered rapidly to patients with hypovolemia [6] and for HAT [7] during surgery and anesthesia. The HES administered in this study can be regarded as being used for common acute and massive hemorrhage. As shown in this study (Fig. 1), the prewarmed temperature of HES did not decrease substantially, without any additional warming techniques, when the infusion rate was high (1000–2000 ml·hr^{-1}) [17]. Although the temperature effect of infused fluids appears to be equi-potential whether they remain in the intravascular spaces or in the extravascular spaces [8], HES also has the advantage that the fluid temperature can be kept slightly but significantly warmer than that of crystalloid solution during administration, because HES has a higher specific heat than crystalloid solution [16].

In conclusion, the use of HES packs routinely kept in a warming cabinet prior to surgery and anesthesia can

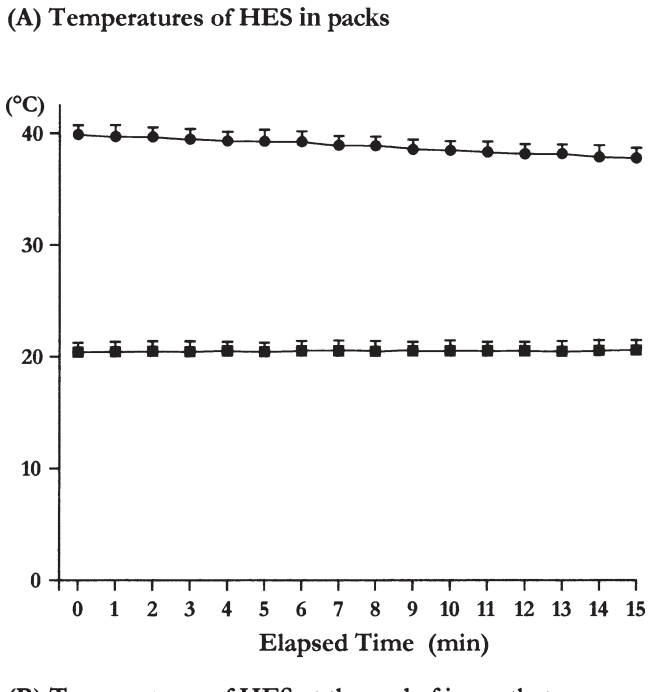

Fig. 1A,B. Time courses of measured temperatures of hydroxyethyl starch (*HES*) in packs (**A**) and at the end of 1-m intravenous tubing connected to the central venous catheter (**B**) for the first 15 min (one 500 ml pack). *Closed circles*, temperature in the warmed group, for which HES packs had been kept in a warming cabinet; *closed squares*, temperature in the control group, for which HES packs were kept at room temperature. Values are means ± SD; $n = 10$ in each group

maintain warm body temperature, easily, safely, and effectively.

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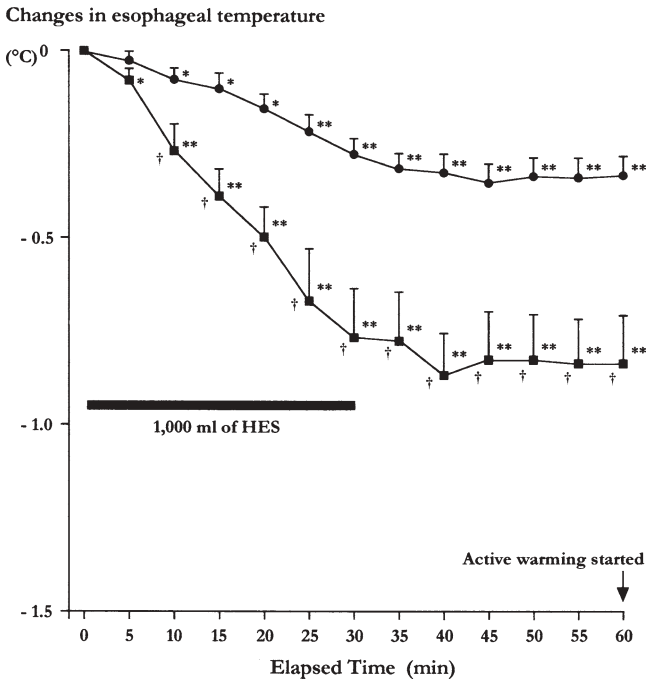

Fig. 2. Time courses of changes in esophageal temperature, measured as the core temperature. *Closed circles*, temperature changes in the warmed group, for which HES packs had been kept in a warming cabinet; *closed squares*, temperature changes in the control group, for which HES packs were kept at room temperature. Values are means ± SD; $n = 10$ in each group. * $P < 0.05$; ** $P < 0.01$ vs temperature at the beginning of the study. † $P < 0.05$ vs temperatures in the warmed group

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