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Original article:

A Comparison between Low and High-dose of Hydroxyethylstarch Solution in Resuscitation for Shock induced by Ischemia/Reperfusion in Rabbits

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ABSTRACT

The purpose of the study was to compare the effects of high and low dose of 6% hydroxyethyl starch solution (HES) on resuscitation for shock induced by intestinal ischemia/reperfusion (I/R) injury in rabbits. Thirty-two anesthetized rabbits were randomized into four groups of eight animals each, which was either treated with no fluid resuscitation as control, lactated Ringer's solution (LRS, 20ml/kg/h), LRS+HES (LRS 18ml/kg/h + HES 2ml/kg/h, low dose of HES) or only treated with HES (high dose of HES, 20ml/kg/h). These rabbits underwent the intestinal I/R injury developed by occluding superior mesenteric artery (SMA) with a noncrushing vascular clamp for 60min and then loosing the clamp for 240min. The fluid resuscitation began at the same time of reperfusion. Hemodynamic parameters including MAP, HR, aortic velocity (Qaorta, as CO) and SMA blood flow (Osma) were measured. Tissue oxygenation was assessed indirectly by measuring the tonometric parameters of gut, including difference between intestinal intramucosal $PtCO_2$ and arterial $PaCO_2$ (PCO_2-gap), intestinal intramucosal pH (pHi), arterial lactate acid concentration and oxygen delivery (DO_2). Mortality of the rabbits was calculated at the end. The results showed that hemodynamic parameters were significantly higher in group LRS+HES and HES than in group LRS and control (P<0.05). Low dose of HES was better than high dose of HES in restoring hemodynamic parameters (P<0.05). Low dose of HES could greatly decrease lactate and PCO_2-gap, significantly improve pHi than other three groups (P<0.05), but high dose of HES did not do so, rather, which induced oral and nasal bleeding, even death of some animals. Low dose and high dose of HES significantly improved DO_2 while LRS did not (P<0.05). Therefore low dose of HSE together with LRS was more effective than only high dose of HES or LRS in the resuscitation for shock induced by intestinal I/R injury in rabbits, because hemodynamic parameters increased suitably and tissue oxygenation was greatly improved.

Keywords: Hydroxyethyl starch, intestinal ischemia/reperfusion injury, shock, fluid resuscitation

INTRODUCTION

Oxygen free radicals, cytokines, histamine, nitric oxide and local acid products could go into systemic circulation within blood flow after intestinal ischemia/reperfusion (I/R). They can increase permeability of microvasculars and result in a decrease of the blood volume available in circulation and tissues edema, as well as hypovolemic shock. Intestinal wall can be damaged. Translocation of bacteria and LPS from the gut can also result in septic shock or systemic inflammatory response syndrome (SIRS) (Deitch 1990; Aydemir-Koksoy et al. 1999). Therefore it is important to perform a seasonable fluid resuscitation. Resuscitation is actively performed for traumatic and hemorrhagic shock in clinic (Soucy et al. 1999; Mauritz et al. 2002), but how to do resuscitation for the intestinal I/R-induced shock is not seriously treated. Hydroxyethylstarch (HES) solution, as artificial effective colloids, is increasingly prescribed in clinic. We hypothesized that different dose of HES has different effects on resuscitation for shock. Thus, in the present study, a comparison between crystalloids and colloids (low and high dose 6% HES, Elohaes, Fresenius, Germany) was made during resuscitation for shock induced by the gut I/R injury in rabbits. We hope to give some experimental evidence for an optimal regimen of fluid resuscitation for shock in acutely ill patients.

MATERIALS AND METHODS

Experimental Preparation

This study was approved by the local Institutional Review Board for Animal Care (Brussels, Belgium). Care and handling of the animals were in accordance with National Institutes of Health guidelines. Thirty-two specific pathogen free New-Zealand rabbits (2.8-3.5 kg body weight) were included in the study. Intramuscular injection of a mixture of ketamine 20mg/kg and xylazine 5mg/kg was given to each animal for sedation and anesthesia, followed by a continuous infusion of ketamine 70mg/kg/h in the first 2 to 4 hours, and of the mixture of ketamine 70mg/kg/h and xylazine 1.5mg/kg/h after 2 to 4 hours through the left ear vein, using an intravenous catheter (Surflo I.V. catheter, 18G x 2) connected by an infusion pump (perfusor® Seura, Braun, Melsungen AG, Germany). Tracheotomy was performed and the animals were mechanically ventilated (Servo ventilator 900B, Siemens-Elema, Solna, Sweden) with 40-60% FiO_2, tidal volume of 7 to 8 ml/kg and a respiratory rate of 35-40 breaths/min, which was further adjusted to maintain a PaO_2>90mmHg and $PaCO_2$ 35-40 mmHg (PCO_2, 47210A Capnometer, Hewlett-Packard, Waltham, MA). Muscle paralysis was obtained by the administration of pancuronium bromide 0.1mg/kg/h at the beginning of the experiment. A 16-G polyethylene catheter was inserted into the right carotid artery and connected to a pressure transducer for recording arterial pressure and withdrawing blood samples. Another catheter (Surflo I. V. catheter, 22Gx2) was placed in the left jungular vein for venous access. A midline laparotomy was performed. The origin of superior mesenteric artery (SMA) was occluded with a noncrushing vascular clamp for 60 min ischemia and then the clamp was loosened for 240min reperfusion. At the same time, ultrasonic flow probes (Transonic System Inc., Ithaca, NY) were placed around SMA (Qsma) and the abdominal aorta (Qaorta) just above the origin of the celiac trunk to continuously measure flow. A tonometric catheter (TRIP® Tonometry Catheter, Datex, Finaland) was inserted into the ileum to measure ileal intramucosal carbon dioxide tension ($PtCO_2$) and intramucosal pH. Body temperature was maintained with a heating lamp. Fluid maintenance was approximately lactated Ringer's solution at 4ml/kg/h during the course of surgery and 60min ischemia.

Experimental Protocol

The rabbits were randomly divided into four experimental groups of eight animals each.

Group1 (model control): a fluid maintenance

of 4ml/kg/h (lactated Ringer's solution) was continuously kept during 240min reperfusion.
Group 2 (resuscitation of lactate Ringer's solution, LRS): a continuous intravenous infusion of LRS 20ml/kg/h.
Group 3 (LRS plus low dose HES): a continuous intravenous infusion of LRS 18ml/kg/h and 6%HES 2ml/kg/h
Group 4 (high dose HES): an intravenous infusion of 6% HES only 20ml/kg/h.
The above fluid resuscitations were immediately performed while the clamp was loosened.

The animals were allowed to recover for 60min before starting the experimental protocol. Hemodynamic measurements and blood samples were obtained at baseline and ischemia of 60 min, reperfusion of 30 min, 60 min, 120 min, 180 min, 240 min in each group. Mean arterial pressures (MAP) were monitored continuously, using a pressure monitoring kit (Baxter, Uden, Holland) with amplifies (Servomed, Hellige, Freiburg, Germany) and a pen recorder (2600S, Gould, Instruments Division, Cleveland, OH). Qsma and Qaorta (as cardiac output) (von Spiegel et al. 1996; Pastor et al. 1994) were simultaneously measured by ultrasound volume flowmeter (T208, Transonic Systems Inc, calibrated by the manufacture). Arterial blood samples were withdrawn for immediate determination of blood gases and blood lactate concentration (ABL625, Radiometer, copenhagen,Denmark).Intestinal intramucosal $PtCO_2$ and pHi were measured by saline tonometry with the standard technique (Creteur et al. 1997; Revelly et al. 1996; Knichwitz et al. 2000). The tonometer balloon was filled with 1ml saline and allowed to equilibrate for 60min. The first 0.7ml aspirated was discarded, and the remaining 0.3ml was immediately analyzed by the blood gas analyzer. The PCO_2-gap was calculated as the difference between $PtCO_2$ and arterial $PaCO_2$. Oxygen delivery (DO_2) was derived from standard equations. The death of the rabbits was calculated at the end of the experiments.

Statistical Analysis

All values are presented as mean ± SD. Significance was tested by T test but animal mortality by X^2 test. $P<0.05$ was considered statistically significant.

RESULTS

The animal model showed some notable characteristic of intestinal I/R injury in group1 (Hill et al. 1993): MAP, HR, Qaorta, Qsma decreased gradually after reperfusion and even three rabbits died during the experiment. Experimental animals began to die after reperfusion of 60min. But there was no death of animals in low dose HES group ($P<0.005$, table 1). No significant difference was observed among the four groups in hemodynamic and metabolic parameters at baseline and ischemic 60min. But all parameters showed great changes during reperfusion of 240min.

Table1: Animals Mortality

Group	Animal number	Dead number	Mortality
Control	8	3	37.5%
LRS	8	2	25.0%
LRS+HES	8	0	0*
HES	8	1	12.5%

$X^2=36.1$, *P<0.005, vs. control

Hemodynamics

Hemodynamic measurements were performed according to experimental protocol. The results showed that the changes of parameters in group 2 were approximately similar to those in group 1 (no significant difference). The decreasing degree in MAP was bated, but HR did not decrease while Qaorta, Qsma increased more in group 3, 4 than in group 1, 2 (P<0.05). The changes of MAP, Qaorta, and Qsma were more stable in low dose HES group than in high dose HES group. MAP decreased after reperfusion of 180 min in group 4 than in group 3 (P<0.05). Qaorta, and Qsma increased greatly after reperfusion of 60 min in group 4 than in group 3 (P<0.05, table 2).

Table 2: Changes of hemodynamic parameters at different time in each group($\bar{X}$ ±S, n=8)

parameters	time（min）	control	LRS	LRS+HES	HES
MAP（mmHg）	baseline	70.0±1.31	71.8±2.55	72.3±6.43	73.1±5.79
	ischemia 60	69.0±6.12	69.3±6.23	67.1±6.31	76.4±7.56
	reperfusion 30	49.3±5.55	48.5±3.70	61.0±4.78*#	66.9±5.77*#
	60	45.6±7.44	38.3±6.63	57.6±7.74*#$	71.1±6.32*#
	120	40.6±8.65	34.1±10.35	65.1±6.58*#$	71.1±13.80*#
	180	32.6±15.04	37.8±8.30	64.5±8.28*#	58.8±15.03*#
	240	32.0±9.92	34.3±9.9	63.6±6.25*#$	52.0±12.50*#
HR (beats/min)	baseline	208.5±20.78	226.1±21.84	207.9±27.06	241.6±26.99
	ischemia 60	190.0±7.87	195.8±10.10	216.1±36.05	225.5±21.04
	reperfusion 30	183.1±11.54	191.8±46.36	211.2±35.31	203.6±28.58
	60	178.0±22.07	192.3±36.85	203.3±22.70	212.6±33.46
	120	180.1±41.74	159.1±39.50	203.5±27.29	204.9±33.99#
	180	127.8±77.52	154.3±18.42	192.1±40.07*	198.5±38.85*#
	240	120.8±19.01	131.0±22.86	182.6±19.13*#	206.1±43.45*#
Qaorta (ml/min)	baseline	77.3±10.40	82.3±15.91	87.6±9.44	96.2±14.60
	ischemia 60	70.1±12.9	64.4±15.80	78.8±13.40	81.1±16.55
	reperfusion 30	35.1±8.22	30.8±11.95	44.8±12.46#$	85.1±27.51*#
	60	28.8±10.55	28.1±8.50	50.7±13.62*#$	82.9±27.88*#
	120	19.3±10.39	28.5±12.06	51.6±17.46*#$	80.5±27.25*#
	180	15.3±11.77	25.0±6.75	48.6±16.35*#	65.3±36.39*#
	240	14.4±9.96	21.3±6.49	49.9±13.21*#	69.7±27.87*#
Qsma (ml/min)	baseline	72.6±8.20	75.8±16.21	74.9±11.97	64.5±18.27
	reperfusion 30	69.9±16.45	67.3±23.99	93.0±25.15	117.6±27.36*#
	60	61.4±23.46	55.9±27.03	95.4±36.94*#$	149.6±51.83*#
	120	53.4±27.06	50.5±28.99	87.1±24.41*#$	168.8±79.09*#
	180	41.9±27.45	49.5±10.96	83.6±18.51*#$	132.3±60.09*#
	240	39.7±17.40	48.4±9.28	76.9±16.43*#$	135.3±73.49*#

*P<0.05, vs. control. , # P<0.05, vs. LRS , $ P<0.05, vs. high dose HES

Blood lactate

A great increase of arterial lactate concentration occurred in group 1, 2. But HES (group 3, 4) significantly limited the

increase in blood lactate concentration. Lactate increased a little in high dose HES group than in group 1, 2(P<0.05), while it increased less in low dose HES group than in other three groups after reperfusion(P<0.05, Fig. 1).

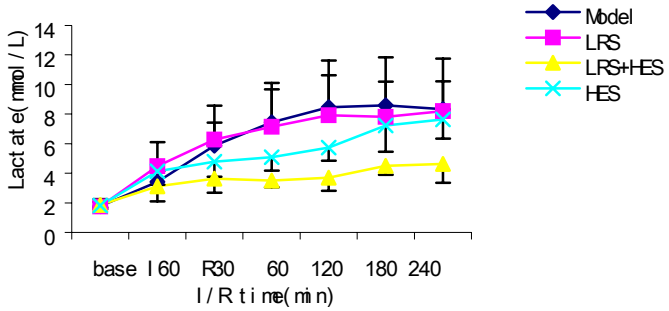

Figure 1: Changes of arterial lactate concentration in the 4 group (n=8 per group). I60=ischemia 60min, R30=reperfusion 30min, *P<0.05, vs. control , # P<0.05, vs. LRS , $ P<0.05, vs. high dose HES.

Tonometry-derived measurements

Resuscitation of low dose HES could significantly decrease PCO_2-gap in the rabbit model of shock. PCO_2-gap greatly increased at 60min ischemia in the four groups. After reperfusion, PCO_2-gap decreased and then increased in group 1, 2, 4 as well, but showed no significant increase continuously in group 3 (P<0.05, Fig. 2).

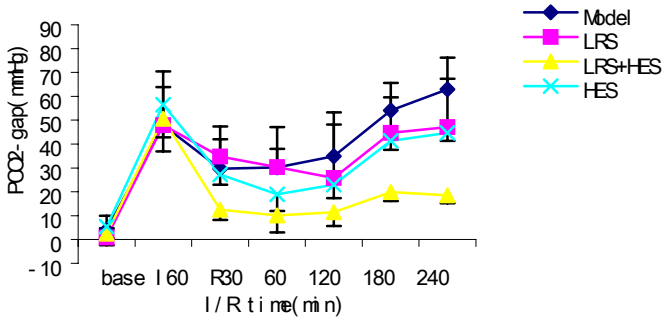

Figure 2: Changes of PCO_2- gap in the 4 group (n=8 per group). See figure 1 for symbols.

Intestinal intramucosal pH

pHi decreased at 60min ischemia in four groups. And then a continuous decrease was present only in group 1, with a little increase in group 2, 4, and a great increase in group 3 after reperfusion (P<0.05, Fig. 3).

Oxygen delivery

DO_2 decreased greatly during I/R in the four groups. But HES (group 3, 4) could significantly attenuate the decrease of DO_2 than in group 1, 2 (P<0.05, Fig. 4). There were no significant differences in the oxygen delivery between high dose HES group and low dose HES group.

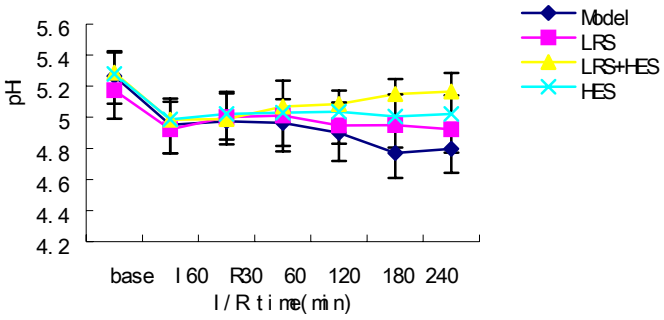

Figure 3: Changes of intestinal intramucosal pH in the 4 group (n=8 per group). See figure 1 for symbols.

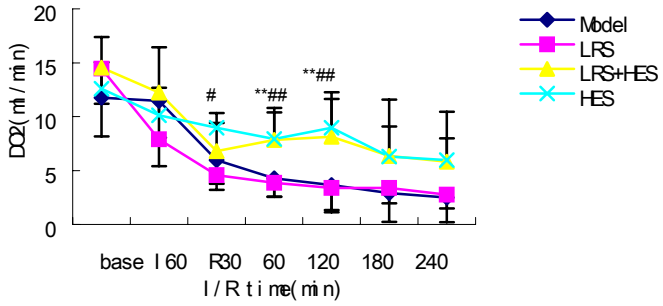

Figure 4: Changes of DO_2 in the 4 group (n=8 per group). See figure 1 for symbols.

DISCUSSION

Intestinal I/R injury, one of the clinical emergency cases of acute illness, can lead to death because of shock, SIRS or multiple organ failure. Thus it is important for the use of fluids resuscitation to prevent the vicious cycle of the disease course. The present study compares the effects of resuscitation for intestinal I/R induced-shock among crystalloids (LRS), high dose HES and low dose HES (LRS+HES). The results show that animal death was presented during 240min reperfusion. The mortality was 37.5% in model control group without resuscitation, 25% in LRS resuscitation group, 12.5% in high dose HES group. No animal death occurred and hemodynamic parameters (MAP, HR, CO, Qsma) were stable in low dose HES group. Low dose HES could better maintain superior mesenteric blood flow, reflecting an improvement in splanchnic perfusion. Thus, the experiment suggested that the effects of resuscitation with mixtures of low dose HES plus LRS were better than with high dose HES or LRS only.

We investigated the effects of different fluid resuscitation on intestinal intramucosal perfusion and oxygenation. The results showed that 6% HES could decrease blood lactate concentration and PCO_2-gap, increase pHi and oxygen delivery after reperfusion, which indicated that HES could improve not only hemodynamic parameters but also splanchnic perfusion and oxygenation in shock induced by intestinal I/R. The results were agreed with what Friedman Z presented in the resuscitation for an uncontrolled hemorrhagic shock in dogs model (Friedman et al. 2003). The mechanisms may be related with HES enhancing blood volume available in systemic circulation and regional blood perfusion (Frumento et al. 2002).

Microcirculative dysfunction in shock is due to the release of a lot of cytokines and various vasoactive substances resulting in to hypoperfusion state of capillary and cell adhesion. Several studies of Collis R.E. et al. have shown that hydroxyethyl starch can repress endothelial cell activated and adhesion molecules (P-selectin) expressed, decrease adhesion molecules concentration in circulative blood in septic shock patients (Collis et al. 1994; Boldt et al. 1996). In sheep models of septic shock due to peritonitis, Morisaki H. et al. confirmed that HES could protect the perfection of capillary, attenuate fluid leak from capillary due to vascular leak syndrome (Morisaki et al. 1994; Yeh et al. 1992; Hakaim et al. 1994; Hasibeder et al. 2002; Pascual et al. 2001) and dilute blood and decrease blood condensation reflecting better splanchnic microcirculation, greater oxygen delivery and tissue hypoxia improved (Deb et al. 1999; Driessen et al. 2003). It might be due to the above mechanisms that HES could improve splanchnic perfusion and oxygenation in our study. In addition, several studies reported that HES could inhibit collection of platelets and damage coagulation (Kapiotis et al. 1994; Baldassarre et al. 1997) leading to bleeding. It is perhaps related with the effects of HES to the oral and nasal bleeding of animals in high dose HES group of the present study.

The figure of 6% HES is an artificial colloid. It has averaged molecular weight of 200,000 daltons and half-life of 3.35 hours in the body. It can be kept in vascular after vein infusion, leading to the plasma colloid osmotic pressure (COP) and blood volume increased (Mena et al. 2000), fluid leak out of vascular forbidden and the blood volume available in circulation increased. These effects can attenuate tissue edema induced by a single infusion of crystalloids (Frumento et al. 2002) and improve splanchnic perfusion and oxygenation (Paes-da-Silva et al. 2003; Wettstein et al. 2004; Wettstein et al. 2003). HES have been extensively used in resuscitation for acute hypovolumic shock because it can restore hemodynamic parameters and oxygen delivery efficiently (Boldt et al. 1996; Nagy et al. 1993). But infusion of high dose HES can increase COP in blood vascular resulting in tissue water flowing back into the vascular and the arterioles dilated apart from the fact that coagulative function is directly damaged (Kapiotis et al. 1994; Baldassarre et al. 1997). Secondary bleeding may also happen because a fast blood flow ould bring about some smashed microthrombus, and coagulative factors were rarefied (Riddez et al. 1998; Onen et al. 2003; Rafie et al. 2004). The mechanisms were confirmed through the comparison of 6% HES of high dose and low dose in the present resuscitative regimen. High dose HES could significantly increase hemodynamic parameters before reperfusion of 120min and then decrease them up to animal death. The pHi increased only a little, PCO_2-gap and lactate concentration showed first decreasing and then increasing in high dose HES group. These might be related with HES leading to bleeding. Low dose HES plus LRS could overcome the weak point of tissue edema induced by crystalloids leak, and also attenuate the side effects of coagulative dysfunction by using high dose HES only. Therefore stable hemodynamic parameters appeared effectively, pHi and DO_2 increased greatly, lactate and PCO_2-gap decreased significantly, as a result, no animals died in low dose HES Group. The better effects could be shown in the resuscitation with low dose HES added by lactated Ringer's solution.

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