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ORIGINAL RESEARCH

Hydroxyethyl starch impairs renal water reabsorption in patients with cardiac shock

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Abstract

Hydroxyethyl starch (HES) has been shown to be correlated with increased risk of renal dysfunction. While almost all articles focus on the side effect of HES on glomerular filtration function, it is barely known to us about the effect of HES on renal water reabsorption. The objective of this study is to assess the effect of HES on renal water reabsorption in patients with cardiac shock. In a retrospective cohort-study, 162 patients admitted to the department of cardiology and diagnosed as cardiac shock were randomized into four groups, depending on different treatments of NaCl (NaCl group), HES (HES group), HES and dopamine (HES + DOP group), HES and norepinephrine (HES + NE group). Data collected included age, sex, blood pressure, heart rate, left ventricular ejection fraction, serum creatinine, blood urea nitrogen, urine specific gravity, urine volume, oxygen saturation serum, drug dosage, and so on. Indices related to renal function were recorded before and after the anti-shock treatments. The comparison was performed among four groups at day 0 or at day 3, and indices of the same group were compared between day 0 and day 3. We found that HES and norepinephrine reduced the urine specific gravity in HES group (day 0 vs day 3, 1.019 $\pm$ 0.006 vs 1.012 $\pm$ 0.005, $p < 0.001$) and in HES + NE group (day 0 vs day 3, 1.019 $\pm$ 0.006 vs 1.011 $\pm$ 0.004, $p < 0.001$). Dopamine increased the urine volume of HES-treated patients at day 3 ($p < 0.001$), and in the meantime dopamine preserved urine specific gravity during anti-shock treatment at day 3 ($p = 0.13$). In conclusion, hydroxyethyl starch caused injured function of renal water reabsorption, and dopamine protected renal water reabsorption in HES-treated patients via increased renal blood.

Keywords

Hydroxyethyl starch; Dopamine; Cardiac shock; Renal dysfunction

1. Introduction

Shock is characterized as a clinical complication of circulatory failure, generally indicating critical condition in patients [1, 2]. It has been shown that patients who develop shock have a significantly higher mortality rate. Shock statistically accounts for 20% deaths in intensive care unit and more than 40% deaths in patients with previous shock [3]. What's more, cardiac shock increases mortality rate to 50%–60% further [4]. The therapeutic strategy in practice is to give priority to high-risk patients and to take effective and efficient measures.

Vasoactive medication and fluid resuscitation are two primary types of anti-shock strategies [2, 5]. Dopamine as one of the vasoactive medicines augments myocardial contractility and systemic vascular resistance, leading to increased cardiac output. Activated dopamine receptor at low doses of dopamine (below 4 μg/kg/min) produces effects of splanchnic and renal vasodilation, increased urine output and renal blood flow, exerting protective effect on kidneys [3]. Norepinephrine induces adrenergic receptor-mediated vasoconstriction and inotropy, consequent to increased tissue perfusion [6]. Colloid plays an important role in volume resuscitation, significantly improve hemodynamic status. One of the most commonly used colloid for fluid resuscitation is hydroxyethyl starch (HES), restoring blood volume and maintaining tissue perfusion quickly [7]. However, the potential toxic effect of HES, especially the risk of renal dysfunction and increased mortality, has hindered the clinical application. As almost all the published papers focus on the adverse effects of HES on glomerular filtration function of renal function [8, 9], the effect of HES on renal water reabsorption has not thus far been investigated.

We hypothesized that HES would impair renal water reabsorption, and dopamine could reduce the risk of renal dysfunction in critically ill patients with cardiac shock. Our study was a retrospective cohort study of investigating effects of HES on renal water reabsorption.

2. Methods

This trial was approved by Shanxi Bethune Hospital Ethics Committee. The committee's reference number of the ethics committee is YXLL-KY-2021-002. The research is in accordance with the Helsinki Declaration of 1975, as revised in 2010. Data collection was in accordance with Bavarian law (BayKrG, Art. 27).

2.1 Study population

A retrospective cohort was constructed of all patients with cardiac shock admitted to the Cardiology Department in Shanxi Bethune Hospital and in the affiliated hospital of Army Medical University NCO School between January 2010 and December 2020. All written informed consent was obtained from participants. Cardiac shock was primarily judged by their treating clinician, depending on factors (such as blood pressure $<$90/60 mmHg, left ventricular ejection fraction $\leq$40% (LVEF), acute myocardial infarction or chronic heart failure).

234 patients were randomized into four groups (NaCl group, HES group, HES + DOP group, HES + NE group) according to the treatment. Patients with cardiac shock received fluid resuscitation firstly. When fluid resuscitation was not enough to alleviate shock, vasoactive agents were titrated to patients, restoring tissue perfusion. In detail, patients admitted in hospital firstly received fluid resuscitation (HES or NaCl). If hemodynamics of these patients was maintained well, these patients were assigned into HES group and NaCl group. If some of them are hemodynamically not stable, and fluid resuscitation was not enough to alleviate shock, vasoactive agents (dopamine or norepinephrine) were titrated to patients, restoring tissue perfusion. Those patients are assigned into HES + DOP group and HES + NE group. Seventy-two patients were excluded because of death in the first 24 hours (n = 10) or prior renal dysfunction (n = 62).

Patients in NaCl group received 0.9% sodium chloride. Patients in HES group received 6% HES with a molecular weight of 130 kD and molar substitution ratio of 0.4 (130/0.4) in 0.9% sodium chloride. Patients in HES + DOP group received dopamine and HES (130/0.4), and ones in HES + NE group received norepinephrine and HES (130/0.4).

2.2 Protocol

The protocol was initiated after patients admitted to hospital before the occurrence of cardiac shock, depicted as first phase (D0). Data collected included age, sex, blood pressure, heart rate, left ventricular ejection fraction, serum creatinine, blood urea nitrogen, urine specific gravity, urine volume, oxygen saturation serum, drug dosage, and so on. The anti-shock treatments were terminated when patients were hemodynamically stable (such as blood pressure $\geq$90/60 mmHg). The stage that three days after the hemodynamic stability of patients depicted as second phase (D3). The reason we collected data 3 days after anti-shock treatment is that almost no residue of HES, dopamine or norepinephrine in circulation might influence the evaluation of renal function. Data related to renal function were recorded at both phases.

2.3 Statistics

Quantitative variables are expressed as mean $\pm$ standard deviation, and qualitative variables are expressed as frequency (percentage) and analyzed using a chi-square test. Normally distributed data were analyzed by two-sided unpaired Student's *t*-test. One-way ANOVA was used to compare means across multiple groups. Statistical analysis was performed using SPSS Statistics Version 18 (IBM Corp., Armonk, NY, USA), and a two-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1 Patient population and baseline patient characteristics

In this study 234 patients were initially screened for eligibility, of which 72 patients were excluded because of death or renal dysfunction. 162 patients were randomized into four groups with different anti-shock treatments (Fig. 1).

Baseline patient characteristics were described in Table 1. The four groups had similar characteristics at baseline. After statistical analysis, we found that there were no differences among four groups in characteristics (such as gender, age, left ventricular ejection fraction, heart rate, blood pressure or oxygen saturation) ($p > 0.05$). Coronary artery disease was the high-risk factor of cardiac shock, and the prevalence of this disease was almost the same as each other among four groups ($p > 0.05$). The morbidity rates of both diabetes and hypertension were also statistically not different in four groups ($p > 0.05$).

3.2 The effect of different anti-shock treatments on renal function

HES was administered to patients in three groups. Total HES use was 2144.83 $\pm$ 1464.85 mL in HES group, 2101.24 $\pm$ 1680.17 mL in HES + DOP group, and 2179.79 $\pm$ 1529.48 mL in HES + NE group. No difference of HES dosage was observed in groups ($p > 0.05$). 0.9% NaCl solution (3518 $\pm$ 1223.52 mL) was provided to patients in NaCl group. While intravenous fluid therapy (HES solution) could not improve hemodynamics in patients with shock, patients in HES + DOP group received dopamine (552.19 $\pm$ 252.15 mg), and patients in HES + NE group received norepinephrine (21.52 $\pm$ 8.59 mg) (Table 2).

The serum creatinine (Scr) and blood urea nitrogen (BUN) of patients at D0 phase were similar in four groups ($p > 0.05$). Different treatments including fluid resuscitation (NaCl, HES) and vasoactive agents (dopamine and norepinephrine) did not influence the Scr and BUN in patients at D3 phase ($p > 0.05$). However, NaCl solution and dopamine + HES resulted in more urine volume at D3 phase than that at D0 phase ($p < 0.001$). While NaCl solution and HES + dopamine did not influence urine specific gravity ($p > 0.05$), HES and norepinephrine reduced the urine specific gravity at D3 phase in HES group (1.019 $\pm$ 0.006 vs 1.012 $\pm$ 0.005, $p < 0.001$) and in HES + NE group (1.019 $\pm$ 0.006 vs 1.011 $\pm$ 0.004, $p < 0.001$) (Table 3).

There was a high incidence of hypokalemia and hypona-

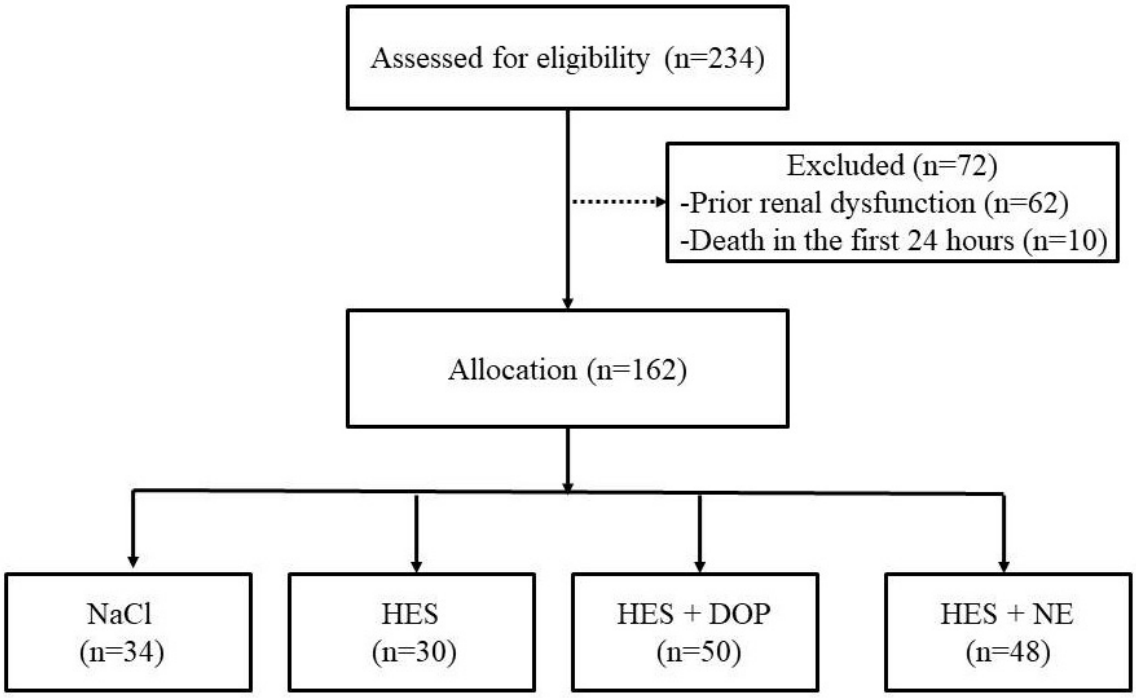

FIGURE 1. Patient population. Patients were randomized into four groups with different anti-shock treatments. Values are number.

TABLE 1. Baseline patient characteristics of four groups.

		NaCl	HES	HES + DOP	HES + NE	*p*
Age (yr)		64 ± 11	65 ± 16	65 ± 13	67 ± 14	0.57
Gender						
	Male	20 (58%)	16 (53%)	26 (52%)	23 (48%)	
	Female	14 (41%)	14 (47%)	24 (48%)	25 (52%)	0.81
LVEF (%)		33.54 ± 3.84	31.87 ± 4.03	35.53 ± 4.11	31.63 ± 3.97	0.45
Diabetes		11 (32%)	10 (33%)	20 (40%)	18 (38%)	0.58
Hypertension		28 (82%)	23 (77%)	42 (84%)	40 (83%)	0.59
Coronary artery disease		30 (88%)	25 (83%)	44 (88%)	41 (85%)	0.68
Heart rate (bpm)		87 ± 12	90 ± 12	88 ± 11	92 ± 12	0.42
Mean blood pressure (mmHg)		80 ± 9	78 ± 8	78 ± 8	79 ± 7	0.72
Oxygen saturation (%)		94.01 ± 2.65	93.54 ± 2.43	94.14 ± 2.30	94.51 ± 2.71	0.76

There were no differences in baseline patient characteristics among four groups. Values are expressed as mean ± SD or number (percentage) where appropriate. LVEF, left ventricular ejection fraction.

tremia in patients with cardiac shock. What's more, patients receiving anti-shock treatments were more prone to suffering from hypokalemia ($p < 0.05$) (Table 3).

4. Discussion

HES-related renal dysfunction is the primary concern that hinders the application of HES in clinic. In this study, we found HES damaged the function of renal water reabsorption. However, when dopamine was jointly given to patients with cardiac shock, renal water reabsorption can be preserved. Therefore, we expect that HES is used jointly with dopamine to treat patients with cardiac shock, decreasing the risk of renal dysfunction.

4.1 HES is cautiously used clinically with regard to adverse effect on renal function

HES solution as a less-expensive synthetic colloid to albumin is widely used in clinical practice, aiming at restoring intravascular volume [10, 11]. The toxicity of HES results from the cumulative tissue uptake. HES can be detected in plasma, urine and tissues (such as liver, muscle, spleen and skin) on the first day after infusion, associated with impaired coagulation, renal injury and severe persistent pruritus [12]. Endothelial and epithelial cells in proximal kidney tubule have been reported to participate in the ingestion of HES [12]. *In-vitro* studies

TABLE 2. Summary of drug use.

	NaCl	HES	HES + DOP	HES + NE	*p*
HES (mL)		2144.83 ± 1464.85	2101.24 ± 1680.17	2179.79 ± 1529.48	0.97
DOP (mg)			552.19 ± 252.15		
NE (mg)				21.52 ± 8.59	
NaCl (mL)	3518 ± 1223.52				

HES, hydroxyethyl starch; DOP, dopamine; NE, norepinephrine; Values are expressed as mean ± SD.

TABLE 3. The effect of different treatments on renal function and electrolyte.

	NaCl	HES	HES + DOP	HES + NE	*p*
Scr (μmoI/L)					
D0	65.56 ± 15.29	61.97 ± 13.74	69.00 ± 15.36	70.44 ± 11.88	0.08
D3	71.48 ± 12.86	68.63 ± 13.23	68.54 ± 13.82	72.54 ± 17.94	0.37
p	0.18	0.07	0.84	0.49	
BUN (mmol/L)					
D0	5.57 ± 1.41	5.34 ± 1.05	5.48 ± 1.21	5.31 ± 1.09	0.75
D3	5.68 ± 1.24	5.26 ± 1.13	5.26 ± 1.25	5.29 ± 1.18	0.98
p	0.54	0.71	0.41	0.92	
Urine volume (mL)					
D0	2393.55 ± 465.80	2483.33 ± 503.66	2241.00 ± 379.73	2212.29 ± 425.87	0.09
D3	2907.35 ± 509.33	2526.33 ± 539.31	2730.00 ± 355.49	2344.37 ± 331.80	0.003
p	<0.001	0.65	<0.001	0.53	
Urine specific gravity					
D0	1.020 ± 0.006	1.019 ± 0.006	1.020 ± 0.006	1.019 ± 0.006	0.94
D3	1.020 ± 0.004	1.012 ± 0.005	1.018 ± 0.004	1.011 ± 0.004	<0.001
p	0.74	<0.001	0.13	<0.001	
Hyponatremia (≤135 mmol/L)					
D0	10 (29%)	8 (26%)	14 (28%)	12 (25%)	0.97
D3	23 (67%)	15 (50%)	21 (42%)	27 (56%)	0.13
p	<0.001	0.06	0.14	<0.001	
Hypokalemia (≤3.5 mmol/L)					
D0	7(21%)	5(16%)	10 (20%)	9 (19%)	0.98
D3	28(82%)	12(40%)	28 (56%)	25 (52%)	0.01
p	<0.001	<0.001	<0.001	<0.001	

Scr, The serum creatinine; BNU, blood urea nitrogen. Values are expressed as mean ± SD or number (percentage) where appropriate.

have confirmed that HES impairs the endothelial barrier but not epithelial barrier, and side effects of HES are correlated to reduced cell-matrix or cell–cell adhesion [11]. Several HES products have been developed in recent years, differing from each other in molecular weight, degree of substitution, and hydroxyethylation ratio [11, 13]. Lower molecular weight of HES seems to lead to increased tissue uptake [12].

In this study we found that NaCl solution did not affect urine specific gravity, and HES reduced urine specific gravity. Therefore, we thought that HES impairs renal water reabsorption of kidney tubules. When water reabsorption is impaired, it is reasonable to speculate that the urine volume will be increased. In our study, we found reduced urine specific gravity and no increased urine volume in HES group and HES + NE group. I think there are some reasons: (1) when plenty of HES solution is transfused into circulation, it will lead to increased plasma colloid osmotic pressure and decreased glomerular effective filtration pressure. The consequence is that more water is preserved in circulatory system, and less water is filtered and eliminated to the outside of the body. Although we found HES impaired water reabsorption and decreased urine specific gravity, the effect of decreased glomerular effective filtration pressure and reduced urine specific gravity compensated each other, leading to no change in urine volume of HES group. (2) Norepinephrine activates α1 adrenergic receptor, producing decreased renal blood flow in HES + NE group. When renal

blood flow decreases, glomerular effective filtration pressure will further reduce, inducing less urine volume. So we did not find increased urine volume in HES group and HES + NE group.

The normal range of urine specific gravity is 1.015 to 1.025. There are also some experts considering the value of 1.010 to 1.025 as normal range in healthy persons. In this trail, we found urine specific gravity decreased to 1.012 ± 0.005 in HES group and to 1.011 ± 0.004 in HES + NE group after anti-shock treatments, which is still in normal range. However, there is statistically significant difference after treatments. Technically, it is reasonable to conclude that HES impairs renal water reabsorption. If we prolong the study period, maybe we can obtain the decreased value of urine specific gravity below the lower limit.

Interestingly, hypokalemia and hyponatremia are common in patients before and after anti-shock treatments. It is reasonable to speculate that reduced urine specific gravity and increased urine volume may worsen electrolyte imbalance.

A survey revealed that 66% of physicians believed HES solution improves survival rate of patients [12], and HES accounted for 43% of colloids to improve abnormal perfusion and vital signs [10]. However, the use of HES in critical care has been shown to be associated with increased risks of kidney failure, renal replacement therapy and mortality [10]. Some organizations (e.g., European Society of Critical Care Medicine and European Medicines Agency) recommended the avoidance of HES in patients with renal dysfunction or sepsis or burn injuries or critical ill [9], whereas the American Thoracic Society Guidelines advise cautious use of HES in critically ill patients [10]. A lot of effort has been given to balance the safety and efficacy of HES. The latest balanced HES 130/0.4 was developed in 2001, but until now clinical evidence is not adequate to conclude that HES 130/0.4 is safer than other HES products [10]. Generally HES is still administered to critically ill patients despite of the increased risk of kidney dysfunction and mortality [14], and a consensus has been reached world widely that renal function must be monitored in HES-treated patients [8, 15].

4.2 Dopamine plays a protective role on renal function in HES-treated patients

When fluid resuscitation is not able to restore tissue perfusion and arterial pressure (<80–85 mmHg) [16], vasoactive agents should be administered immediately in patients with cardiac shock [3]. By stimulating receptors in the heart and vessels, vasoactive agents produce direct inotropic effect and peripheral vascular effect, increasing cardiac output and systemic vascular resistance [3, 17], which, in turn, preserves visceral perfusion [16].

Different dose of dopamine activates dopaminergic receptors, $\beta 1$ adrenergic receptors and $\alpha 1$ adrenergic receptors, resulting in natriuretic effects and increased cardiac output and systemic vascular resistance [3]. Activated dopaminergic receptors lead to increased renal blood and creatinine clearance [18]. The mechanism of HES-related renal toxicity is that luminal epithelial cells in the proximal tubule can take up HES molecules by pinocytosis, impairing renal function [12, 18]. Our study elucidated the protective role of dopamine on renal water absorption in HES-treated patients. We thought the underlying mechanism is that: activated dopamine receptors increase renal blood flow and then inhibit the process of epithelial cells absorbing HES, preserving the function of proximal tubule and reducing the toxicity of HES on kidney. Therefore, we recommend joint use of dopamine and HES in patients with cardiac shock, to decrease the risk of renal failure.

Norepinephrine is regarded as the first-line vasopressor for shock. Norepinephrine is approximately 100 times the potency of dopamine [3]. However, excessively activated-$\alpha 1$ adrenergic receptor produces decreased renal blood flow, predisposing to kidney injury [19]. Considering the risk of precipitating acute renal failure, clinicians are hesitant to choose norepinephrine [20]. Our study found the combined utilization of HES and norepinephrine led to decreased urine specific gravity, suggesting injured renal water absorption. While HES alone has a toxic effect on renal function, we postulate that the joint use of norepinephrine may aggravate renal ischemia, inducing increased risk of renal injury. Therefore, we recommend norepinephrine not be jointly used with HES during anti-shock treatment.

5. Limitation

Researchers have reported that HES-treated patients demonstrated increased risk of renal failure and mortality. In our study, we did not find any patient showed increased Scr or BUN after the treatment of HES. The reason may be that we did not collect the clinical data over a longer period. Many researchers did not terminate the experiments until 90 days after the treatment of HES [21, 22]. In this trial, we collected data in the phases of before the occurrence of cardiac shock and three days after the anti-shock treatment. Generally, almost all data were collected in less than three weeks in our study. So it is obvious that our study has been ended before reduced glomerular filtration rate occurs. Therefore, in this study we did not find the effect of HES on glomerular filtration rate. It is reasonable in late-stage trial to prolong this study to three months, investigating the effect of HES on glomerular filtration function and renal water reabsorption.

6. Conclusions

It is widely known that HES is associated with increased risk of renal injury, and a lot of published work has been done to investigate the effect of HES on glomerular filtration function. However, glomerular filtration function is only one of the primary renal functions. It is barely known to us about the effect of HES on renal water reabsorption. Therefore, we were engaged to conduct this study.

In the present study, the major novelty is that we found intravenously infused HES was associated with deleterious impact on renal water reabsorption. While the combined use of dopamine increased urine volume, dopamine could spare the adverse effect of HES on patients, protecting renal function of water reabsorption. In the regard of this finding, we advise that when HES is given to patients with cardiac shock, it is reasonable for doctors to administer dopamine simultaneously,

to decrease the risk of renal dysfunction.

AUTHOR CONTRIBUTIONS

ZJY wrote the manuscript. ZX, CML, ZYG and MG participated in the statistical analysis. ZJY, ZS, ZGW designed the study. DJH reviewed the final version of the manuscript. All authors participated in the acquisition of data. All authors have browsed and agreed the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All written informed consent was obtained from participants. This trial was approved by Shanxi Bethune Hospital Ethics Committee. The committee's reference number of the ethics committee is YXLL-KY-2021-002. The research is in accordance with the Helsinki Declaration of 1975, as revised in 2010. Data collection was in accordance with Bavarian law (BayKrG, Art. 27).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

CONSENT FOR PUBLICATION

All the authors have approved the manuscript and agree with submission.

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