Comparison of the novel hydroxyethylstarch 130/0.4 and hydroxyethylstarch 200/0.6 in brain-dead donor resuscitation on renal function after transplantation

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Background. The renal effect of hydroxyethylstarch (HES) solutions remains controversial. We hypothesized that the use of HES with a mean molecular weight of 130 kDa would reduce renal dysfunctions in the recipients. Our study was aimed at comparing the effects of two fluid regimens (HES 130/0.4 or HES 200/0.6) used for the resuscitation of brain-dead donors on the rate of delayed graft function (DGF) and the serum creatinine levels post-transplantation.

Methods. This retrospective matched-paired study was conducted in an intensive care unit of a university hospital. Case–controls were matched at the donor patient level as follows: gender, BMI, duration of ICU stay, serum creatinine levels, vasopressor, and volume of colloids. The organ donation from 64 brain-dead donors resulted in 115 transplants.

Results. The renal function was similar among all donors. The characteristics of the recipients, including the cold ischaemia time, were similar. The rate of DGF was 22% in the donors treated with HES 130/0.4, compared with 33% in those treated with HES 200/0.6 (P=0.27). The serum creatinine levels at 1 month were 133 (38) μmol litre⁻¹ when the donors had been treated with HES 130/0.4 and 172 (83) μmol litre⁻¹ when they were treated with HES 200/0.6 (P=0.005). A difference was found 1 yr after transplantation [128 (36) vs 147 (43) μmol litre⁻¹, P=0.05].

Conclusions. Using a modern, third-generation, rapidly degradable HES preparation with a low degree of substitution seems to be associated with a better effect on the renal function of recipients.

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Specific risk factors for kidney transplant failure are related to the resuscitation procedure of the brain-dead donor. Among them, the type of fluid used in organ donors is of crucial importance. Hydroxyethylstarch (HES) is hydrolysed in vivo by serum amylase, and then is excreted by the kidney. Plasma accumulation occurs with high molecular weight and highly substituted HES. An important adverse effect of HES solutions is impairment of the renal function. In the field of kidney transplantation, it has been shown that the use of HES is associated with a worsening of graft quality.¹ However, this adverse event was demonstrated with high molecular weight and highly substituted HES (200/0.6). To the best of our knowledge, the effect of novel HES with a mean molecular weight of 130 kDa, a molecular substitution of 0.4 (HES 130/0.4), and a C2/C6 ratio greater than eight remains unknown.

Hence, the actual influence of HES solutions on renal function remains controversial.² The present retrospective study was aimed at comparing the effects of two fluid regimens administered to brain-dead donors on the rate of delayed graft function (DGF) and the levels of serum creatinine after transplantation, using either a 130 kDa HES (HES 130/0.4) (Voluven® 6%, Fresenius Kabi, Sèvres, France) or a 200 kDa HES (HES 200/0.6) (EloheS®,...
Fresenius Kabi France, Louviers, France). We hypothesize that the use of the 130/0.4 HES would reduce the rate of DGF and the increase in serum creatinine levels in the recipients.

Methods

This retrospective study was conducted in a 16-bed intensive care unit (ICU) of a university hospital. Informed consent and approval by the Ethics Committee were waived due to the retrospective nature of the study. A case–control study was elaborated according to a before–after design. Thirty-two donor patients were retrospectively paired-matched for two distinct time periods. The organ donation from the 64 brain-dead donors resulted in 115 renal transplants. The fluid regimen of the controls consisted of HES 200/0.6, which was used from 1998 to 2000. The fluid regimen of the cases consisted of HES 130/0.4, which was used for kidney donor resuscitation from 2004 to 2006. Each case treated with HES 130/0.4 was matched to one control treated with HES 200/0.6 for volume replacement therapy, according to the following criteria: gender, BMI, smoking, preharvesting serum creatinine level, duration of stay in ICU, and volume of colloid.

We investigated the effects of the two fluid regimens (HES 130/0.4 vs HES 200/0.6) on the renal graft quality through two criteria: DGF and serum creatinine levels at 1 month and 1 yr. DGF was defined by the need for dialysis in the 7 days after transplantation.8 These criteria were chosen because chronic rejection is the most prevalent cause of renal transplant failure.9 Chronic allograft nephropathy represents cumulative and incremental damage to nephrons from time-dependent immunologic and non-immunologic causes.10 DGF and serum creatinine levels at 1 yr are associated with renal transplant failure.10 Before testing the effects of the fluid regimens, in order to separate random factors from treatment effects, we compared the serum creatinine levels of the right and left kidneys that came from the same donors.

The indications for fluid resuscitation were left to the attending physician’s discretion. Briefly, these indications were a level of central venous pressure <8 mm Hg, a urine output <0.5 ml kg\(^{-1}\) h\(^{-1}\), echocardiography data with left-ventricular end-diastolic area below 5.5 cm\(^2\) m\(^{-2}\), and variations of pulse pressure >13%. The vasopressors were introduced when mean arterial pressure remained below 65 mm Hg, despite adequate fluid resuscitation.

Data from donors were analysed from ICU admission to kidney removal. We collected sex, age, BMI, causes of ICU admission, duration of ICU stay, duration of brain-death, fluid expansion, vasopressors, haemodynamic profile during ICU resuscitation, and characteristics of renal function on admission and during ICU stay. After data from recipients were analysed: sex, age, BMI, duration of cold ischaemia, renal function post-transplantation evaluated by DGF and serum creatinine levels at 1 month and 1 yr post-transplantation in the patients without recourse to dialysis.

The collected data were entered into a Microsoft® Office Excel 2000, then transferred to SPSS v.11.5.1® software for analysis of the results. Statistical descriptions: quantitative variables are presented in the form of mean (SD). Quantitative data were compared using parametric tests (Student’s t-test or an analysis of variance) or non-parametric tests (Kruskal–Wallis test), as required. Qualitative data are expressed as percentages. They were compared with \(\chi^2\) test or Fisher’s exact test. The threshold for significance of the statistical tests was set at 5%.

Results

Using our matching procedure, we found suitable matches for 100% of our brain-dead donors. Importantly, this matching procedure was done at the donor patient level and not on the recipient level. When compared with the donors treated with HES 200/0.6, the donors treated with HES 130/0.4 were older, and received larger volume of crystalloids (Table 1). The renal function was similar in both groups of donors.

The demographic characteristics of the recipients were similar (Table 2). Of note, the cold ischaemia time was similar in both groups. No significant differences were found in the serum creatinine levels in recipients who received the right kidney, when compared with those receiving the left kidney from the same donors (Fig. 1). The rate of DGF was 19% in the recipients receiving a right kidney compared with 26% in those receiving a left kidney (\(P=0.6\)). Although the rate of DGF was increased in the donors treated with HES 200/0.6, this difference did not reach a significant level (33% vs 22%, \(P=0.27\)). In contrast, the serum creatinine levels at 1 month were lower in the patients treated with HES 130/0.4 than in those treated with HES 200/0.6 [133 (38) vs 172 (83) \(\mu\)mol litre\(^{-1}\), \(P=0.005\)] (Fig. 2). This difference was still observed 1 yr after the transplantation [128 (36) vs 147 (43) \(\mu\)mol litre\(^{-1}\), \(P=0.05\)] (Fig. 2).

Discussion

In this retrospective study, the administration of a fluid regimen containing the HES 130/0.4 was associated with lower serum creatinine levels than that containing the HES 200/0.6. There was a difference in the rate of DGF, which did not reach a significant level. Solutions of HES are synthesized from natural polymers of amylopectin. The pharmacokinetics of HES depends on the degree of substitution at carbons 2, 3, and 6 in the glucose ring in combination with the molecular weight, because the C2/ C6 hydroxyethylation ratio influences their degradation.
mainly by non-specific plasma amylases. The optimum HES solution combines the lowest in vivo molecular weight above the threshold for renal elimination with a low degree of hydroxyethyl substitution. Easily degradable HES solutions, dominated by medium molecular weight, meet these specifications. With regard to safety considerations, HES solutions with a low to medium in vivo molecular weight may offer the best risk to benefit ratio among the available synthetic colloids. Consequently, there is a need to reassess the renal effects of HES regarding their novel pharmacokinetic properties. Our hypothesis was that the novel HES used in the present study may reduce the risk of renal dysfunction, when compared with the high molecular weight solutions used in prior studies.

Table 1 Characteristics of donors. *Oliguria: urine output <0.5 ml kg\(^{-1}\) h\(^{-1}\) for two consecutive hours during ICU stay

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>All patients (n=64)</th>
<th>HES 200/0.6 (n=32)</th>
<th>HES 130/0.4 (n=32)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>44 (69)</td>
<td>22 (69)</td>
<td>22 (69)</td>
<td>0.78</td>
</tr>
<tr>
<td>Age (yr) [mean (range)]</td>
<td>41 (17–82)</td>
<td>36 (18–61)</td>
<td>47 (17–82)</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI &lt;25 kg m(^{-2}) (%)</td>
<td>64 (100)</td>
<td>32 (100)</td>
<td>32 (100)</td>
<td>1</td>
</tr>
<tr>
<td>Head trauma/intracranial bleeding (%)</td>
<td>31 (48)/33 (52)</td>
<td>17 (53)/15 (47)</td>
<td>14 (44)/18 (56)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Timing of ICU steps
- Duration of stay in ICU (h) [mean (so)]
  - HES 200/0.6 (n=32)
  - HES 130/0.4 (n=32)
  - P-value
- Duration of brain death (h) [mean (so)]
  - HES 200/0.6 (n=32)
  - HES 130/0.4 (n=32)
  - P-value

Mean arterial pressure
- Upon admission (mm Hg) [mean (so)]
- Organ removal (mm Hg) [mean (so)]
- Vasopressor (norepinephrine) (n) (%)
- Fluid expansion
- Colloids (ml h\(^{-1}\)) [mean (so)]

Urine output anomaly
- Diabetes insipidus (n) (%)
- Oliguria* (n) (%)

Serum creatinine levels
- Upon admission (\(\mu\)mol litre\(^{-1}\)) [mean (so)]
- Organ removal (\(\mu\)mol litre\(^{-1}\)) [mean (so)]

Blood lactate levels
- Upon admission (mmol litre\(^{-1}\)) [mean (so)]
- Organ removal (mmol litre\(^{-1}\)) [mean (so)]

Table 2 Characteristics of recipients

<table>
<thead>
<tr>
<th>Groups</th>
<th>All patients (n=115)</th>
<th>HES 200/0.6 (n=57)</th>
<th>HES 130/0.4 (n=58)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>79 (70)</td>
<td>44 (77)</td>
<td>35 (60)</td>
<td>0.07</td>
</tr>
<tr>
<td>Age (yr) [mean (range)]</td>
<td>48 (18–75)</td>
<td>46 (18–71)</td>
<td>49 (19–75)</td>
<td>0.30</td>
</tr>
<tr>
<td>Cold ischaemia time (h) [mean (so)]</td>
<td>18 (6)</td>
<td>19 (5)</td>
<td>18 (7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Delayed graft function (%)</td>
<td>32 (28)</td>
<td>19 (33)</td>
<td>13 (22)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Fig 1 Levels of serum creatinine at 1 month and 1 yr post-transplantation in the recipients receiving either the right or the left kidney (n=42). Groups were compared using Kruskal–Wallis test.

Fig 2 Box and whisker plots illustrate the distribution of serum creatinine levels measured in the recipients at 1 month and 1 yr post-transplantation. Line in the box, median; box borders, 25th and 75th percentiles; whiskers, minimum and maximum. Exceeding values: o >1.5 box length. Groups were compared using Kruskal–Wallis test.
Concerns about the adverse effects of HES on renal function were first raised by Legendre and colleagues, who reported an association between HES exposure of organ donors and osmotic nephrosis-like lesions in the transplant recipients. These authors retrospectively compared 90 patients from a single institution for two distinct time periods: one before HES was made available for use in France and a subsequent period where HES was widely used. The appearance of osmotic nephrosis-like lesions involving proximal and distal tubules was observed more frequently during the later time period, but without obvious detriment in renal function in the recipients. Similar histological lesions were subsequently reported after aggressive isovolaemic haemodilution with HES in anesthetized dogs. They have also been found with a wide variety of agents, including dextran, immunoglobulin, mannitol, and iodinated contrast agents. In a randomized clinical trial comparing the HES 200/0.6 with gelatin, the HES regimen in brain-dead donors was followed by an immediate impairment of renal function in the recipients with an increased rate of haemodilysis and higher serum creatinine levels. However, a retrospective study using the HES 200/0.6 did not confirm this result.

The present retrospective study seems to confirm a detrimental effect of HES 200/0.6 on the renal function of recipients. The aim of our retrospective study was to compare the effects of two different HES on the renal function of recipients. Several studies compared volume replacement regimens using HES 130/0.4 or high molecular weight HES. Most of these studies found an equivalence of efficacy with a lesser effect on coagulation of HES 130/0.4. With regard to renal function, only few data are available. No differences were observed in head trauma patients receiving large dose infusion of HES 130/0.4 or HES 200/0.5. Other authors found that the use of HES 130/0.4 was independently associated with a modest reduction in glomerular filtration rate. For the first time, our results show that HES 130/0.4 have less detrimental effect on renal function than HES 200/0.6.

The present study has several limitations. The retrospective design induced several differences between the patients. Indeed, no randomization between the fluid was performed and several years passed between the inclusion of the HES 200/0.6 patients and the HES 130/04 patients. The treatment groups differ with respect to age, whereas ageing is associated with an increased rate of DGF. The treatment groups also differ with respect to other aspects of the fluid therapy. The volume of crystalloids is larger in the second period than in the first period. This is probably linked to a shorter half-life of HES 130/0.4, when compared with HES 200/0.6. Moreover, changes in treatment may have been introduced during the years intervening the first and second arm of the study. The brain-death duration was shorter in the group treated with HES 130/0.4, when compared with that treated with HES 200/0.6. A prior study shows a lack of correlation between renal function in the recipients and the brain-death duration if the haemodynamics of donors is preserved. Finally, the absence of significant difference in the rate of DGF may be due to the relative small number of patients. Future randomized studies including a large number of patients are required to confirm or not our data.

In conclusion, the influence of different intravascular volume regimens on renal function is still a matter of debate. In the present retrospective study, using a modern, third-generation, rapidly degradable HES preparation with a low degree of substitution (HES 130/0.4) seems to be associated with a better effect on the renal function of recipients. Further studies are needed to clarify the safety of third generation HES preparations with a low degree of substitution in the field of renal transplantation.

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Institution.

**References**


19 Ickx BE, Bepperling F, Melot C, Schulman C, Van der Linden PJ. Plasma substitution effects of a new hydroxyethyl starch HES 130/0.4 compared with HES 200/0.5 during and after extended acute normovolaemic haemodilution. *Br J Anaesth* 2003; 91: 196–202
20 Gandhi SD, Weiskopf RB, Jungheinrich C, et al. Volume replacement therapy during major orthopedic surgery using Voluven (hydroxyethyl starch 130/0.4) or hetastarch. *Anesthesiology* 2007; 106: 1120–7
21 Langeron O, Doelberg M, Ang ET, Bonnet F, Capdevila X, Coriat P. Voluven, a lower substituted novel hydroxyethyl starch (HES 130/0.4), causes fewer effects on coagulation in major orthopedic surgery than HES 200/0.5. *Anesth Analg* 2001; 92: 855–62