

Effect of Hydroxyethylstarch on Renal Function in Cardiac Surgery : a large scale retrospective study

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Summary : *Background :* Recent reports indicated negative effects of hydroxyethylstarch (HES) on renal function. The goal of this large scale retrospective study was to detect whether there was an association between postoperative deterioration of renal function and the use of HES 200 kD, 0.5 DS in the cardiac surgery setting.

Methods : Retrospective analysis of daily collected data in 3124 patients who underwent coronary artery bypass and/or valvular surgery. Three groups were compared according to differences in fluid therapy :

- GEL : gelatin was used as priming fluid of extracorporeal circulation (ECC) and for postoperative filling (n = 1276).
- MIX : HES was used as priming fluid of ECC and gelatin was used for postoperative filling (n = 1008).
- HES : HES was used as priming fluid of ECC and for postoperative filling (n = 840).

Main results : There were no significant differences in postoperative serum creatinine concentrations between the 3 groups : GEL : $12,2 \pm 0,5$ mg/l ; MIX : $12,3 \pm 0,5$ mg/l ; HES : $12,3 \pm 0,6$ mg/l. The need for postoperative extrarenal epuration was not significantly different between the 3 periods : GEL : 2,9% ; MIX : 3,1% ; HES : 3,8%.

Conclusion : The use of HES 200 kD, 0.5 DS in cardiac surgery does not seem to be associated with a clinically significant deterioration of postoperative renal function.

Key-words : Hydroxyethylstarch ; renal function ; cardiac surgery.

INTRODUCTION

Hypovolemia due to bleeding, central blood volume redistribution and diffuse capillary leak is a common cause of post-bypass haemodynamic instability (1, 2). In addition, cardiopulmonary bypass induced diastolic dysfunction further compromises left ventricular preload by enhancing the deleterious effects of any degree of hypovolemia (3). Adequate intravascular volume replacement and blood volume expansion are therefore crucial factors in the maintenance of haemodynamic stability after cardiac surgery. Synthetic colloids as well as crystalloids may be

used as substitution fluids during volume therapy. Among the colloids, the favourable pharmacokinetic characteristics of hydroxyethylstarches (HES) make these solutions particularly attractive for volume expansion in the critically ill (4, 5). Beside negative effects on coagulation, reports indicating deleterious effects on renal function are in part responsible for the lack of general acceptance of HES for volume replacement therapy (6).

Studies dealing with the negative impact of HES on renal function only mention 6% HES with high degree of substitution, Elohes® in septic patients and kidney transplant recipients (7, 8). Moreover, these studies are hampered by the small number of patients. Another study in a larger number of patients treated with 6% HES 200 kD, 0.5 DS reported conflicting results (9).

Acute renal failure (ARF) is one of the most serious complications occurring after cardiac surgery. When severe enough to require dialysis, mortality and morbidity are markedly increased, despite modern techniques of extrarenal epuration and supportive intensive care (10). It is generally accepted that several factors lie at the origin of ARF after cardiac surgery. Advanced age, preoperative disturbed renal function, duration of cardiopulmonary bypass (CPB), type of surgery and postoperative haemodynamic instability can be important factors compromising renal function (11, 12). The possibility of nephrotoxic effect caused by HES used as volume therapy in this particular setting is of major clinical concern. We conducted this large scale retrospective study including 3124 patients in order to look for the possible nephrotoxic effects of HES 200 kD, 0.5 DS used as perioperative volume expander in the cardiac surgery setting.

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Two adaptations in the daily clinical routine, introduction of HES in the priming at first and subsequently also introduction of HES for postoperative volume load, led to three distinctive groups of patients treated differently with respect to fluid administration. This opened the possibility to compare renal and global outcomes between these different groups. The first group (GEL) received gelatines in the priming and for postoperative volume treatment. The second group (MIX) received hydroxyethylstarch in the priming and gelatines for postoperative volume therapy. The third group (HES) received hydroxyethylstarch in the priming and for postoperative volume treatment.

METHODS

Study design

We retrospectively analysed data in 3124 patients admitted in the ICU after cardiac surgery. Data were collected on a daily basis (from January 1993 to December 1999) by the ICU research-staff and were entered into a data base. The patients undergoing coronary bypass and/or valvular surgery (replacement or repair) on cardiopulmonary bypass were included in the study.

We compared three groups according to the kind of colloid used as CPB prime and fluid therapy during the first 24 hours of the ICU stay. The data relative to the three groups were collected during consecutive time periods. The first group (GEL) defined as the "gelatin-group" included 1276 patients in whom gelatin Haemacel® was used as CPB prime and postoperative filling. The second group (MIX) defined as the "mixed-group" included 1008 patients in whom HES 200 kD, 0.5 DS, Haes-Steril®, was used for CPB priming and gelatin for postoperative filling. The third group (HES) defined as the "hydroxyethylstarch-group" included 840 patients in whom Haes-Steril, was used for CPB priming and postoperative filling. Patients who suffered from chronic renal failure requiring preoperative dialysis were excluded from the study (13 patients during the first period, 12 patients during the second period and 9 patients during the third period).

Standard treatment

Priming solution

During the first period, priming solution was made of 100% gelatin. During the second period

priming solution was made of 100% HES. During the third period, priming solution was made of 500 ml HES completed with crystalloids (Plasmalyte®). If needed, red packed cells were used in order to maintain an haematocrit of 20%. Aprotinin (2.10⁶U) and heparin (50 mg) were added to the solution.

Postoperative volume treatment

Clinical criteria for postoperative fluid therapy were: clinical evidence of tissular hypoperfusion, urinary output < 0,5 ml/kg/hr, systolic blood pressure < 100 mmHg and/or cardiac index < 2,2 l/min/m² and/or mixed venous oxygen saturation < 60% and pulmonary capillary wedge pressure < 16 mmHg. Crystalloids were continuously infused during the perioperative period at a rate ≥ 40 ml/hr. Colloids were used for volume expansion. Gelatin was administered without limit, but 6% HES administration was restricted to an upper-limit in agreement to the manufacturer's recommendations of 33 ml/kg. Red packed cells were administered, if necessary, to maintain hemoglobin concentration ≥ 8 gr/100 ml.

Extrarenal epuration

Extrarenal epuration was performed by continuous veno-venous haemofiltration or intermittent haemodialysis. Clinical criteria for postoperative extrarenal epuration consisted of: 1) refractory metabolic acidosis and/or hyperkalemia ≥ 6 mEq/l and/or pulmonary edema in patients with oligo-anuric acute renal failure, 2) urea blood levels ≥ 1,5 g/l and/or creatinine blood levels ≥ 35 mg/l. No specific "renal protective" measures were taken; routine administration of "renal dose" of dopamine was not performed in any patients.

Outcomes and definitions

- *Comparisons* were made between the three periods. The primary end point was the postoperative course of renal function. The secondary end points were the ICU-stay as an index of global morbidity and the ICU mortality rate.
- *The major risk factors of ARF* were evaluated: age, preoperative renal dysfunction (defined by a serum creatinine level above the upper limit of the laboratory's normal values: 12,1 mg/l), type of surgery (CABG vs valvular surgery), postoperative Apache II score (as an index of global physiologic derangement) and the lowest value of the postoperative mean blood pressure (as an

Table I

Comparisons of risk factors of ARF between the 3 groups ; A II : Apache II score, MAP : lowest value of the mean arterial pressure on the first postoperative day

	«GEL-group» n = 1276	«MIX-group» n = 1008	«HES-group» n = 840	
Age (yr)	63.7 ± 9.8	65.1 ± 9.7	66.1 ± 10.3	ANOVA ; p < 0.005
	p < 0.005		NS	
	p < 0.005			
A II	12.9 ± 3.8	11.4 ± 4.0	12.8 ± 4.3	ANOVA ; p < 0.005
	p < 0.005		p < 0.005	
	NS			
MAP (mmHg)	72.9 ± 25.3	82.8 ± 25.6	72.9 ± 23.9	ANOVA ; p < 0.005
	p < 0.005		p < 0.005	
	NS			

Table II

Comparison of risk factors of ARF between the 3 groups ; preoperative renal dysfunction was defined by a preoperative serum creatinine level > 12,1 mg/l

	«GEL-group» n = 1276	«MIX-group» n = 1008	«HES-group» n = 840	
Valvular operation (%)	25.5	27.6	32.0	Pearson Chi-Square ; P < 0.005
	NS		p < 0.05	
	p < 0.05			
Preoperative renal dysfunction (%)	8.7	9.1	10.1	Pearson Chi-Square ; NS

index of postoperative haemodynamic instability).

- *Postoperative course of renal function* was assessed by means of the diuresis during the first 24 postoperative hours and the serum creatinine concentration at the end of the first 24 postoperative hours.
- *Postoperative acute renal failure* was evaluated using two definitions : 1) a postoperative creatinin serum level ≥ 20 mg/l, 2) the need for postoperative extrarenal epuration.

Statistics

Data are expressed as mean \pm standard deviation. Categorical variables were assessed using chi-square test. One way ANOVA for multiple comparisons was used to analyse continuous variables. In the case of global difference between the three groups, the following comparisons were made : (GEL) vs (MIX), (GEL) vs (HES), (MIX) vs (HES) ; Tukey test was used for the pairwise

comparison. Tests were two-tailed and P < 0.05 was considered as significant.

RESULTS

Risk of ARF

The prevalence and severity of major risk factors of postoperative ARF were compared between the three groups. The data are summarized in table I and table II. Significant differences in age, Apache II score and worst value of mean arterial pressure (MAP) were detected between the three groups.

However, with the exception of age which showed a significant increase over the time, the observed differences were quite small and probably without clinical significance. There were no significant differences in the prevalence of preoperative renal dysfunction between the three periods. The percentage of valvular operations increased signif-

Table III

Comparisons of postoperative diuresis and serum creatinine level (on the first postoperative day) between the 3 groups

	«GEL-group» n = 1276	«MIX-group» n = 1008	«HES-group» n = 840	
Postoperative urinary output (ml/day)	3382 ± 1462	3458 ± 1481	2608 ± 1084	ANOVA ; P < 0.0005
Postoperative serum creatinine level (mg/l)	12.2 ± 0.5	12.3 ± 0.5	12.3 ± 0.6	ANOVA ; NS

Table IV

Comparisons of the percentage of postoperative ARF (defined by a serum creatinine level on the first postoperative day ≥ 20 mg/l) and need for postoperative extrarenal epuration between the 3 groups

	«GEL-group» n = 1276	«MIX-group» n = 1008	«HES-group» n = 840	
Postoperative ARF (%)	3.0	3.2	4.2	Pearson Chi-Square ; NS
Postoperative extrarenal epuration (%)	2.9	3.1	3.8	Pearson Chi-Square ; NS

icantly over the time. Globally, these data suggest a relative increase in the risk of postoperative ARF from the first period to the third one. The patients in the HES-group are therefore already more prone to the risk of ARF as compared to the patients in the GEL-group.

Renal outcome

Significant differences in the urinary output of the first postoperative day were detected between the three groups : diuresis was less in the third group (HES group) in comparison with the two other groups (Table III). There were no significant differences in the postoperative serum creatinine levels between the three groups (Table III).

The percentage of postoperative ARF defined by a postoperative level of serum creatinin ≥ 20 mg/l was not significantly different between the three groups (Table IV). There were no significant differences in the need for postoperative extrarenal epuration between the three groups.

Global outcome

Table IV summarizes the data. The ICU mortality was not significantly different between the three groups. The ICU stay was significantly longer in the MIX-group as compared to the two other groups.

DISCUSSION

The present study showed that no significant difference was found in postoperative serum creatinine levels, incidence of postoperative ARF (defined by a serum creatinine level ≥ 20 mg/l) and need for postoperative extrarenal epuration in patients managed with a HES-based fluid therapy in comparison with patients managed with a gelatin-based fluid therapy in the cardiac surgery setting.

Cardiac surgery patients are at risk of developing postoperative renal failure. Indeed, the risk of developing renal dysfunction after cardiac surgery is rather high, ranging from 5% to 30% according to the criteria used to define this complication (10, 11, 12, 13). Severe ARF requiring dialysis develops in 1% to 5% of cardiac surgery patients (10, 11, 12, 13). The observed rates of ARF and ARF requiring dialysis in the three groups of the present study are well within the reported ranges.

The etiology of postoperative ARF after cardiac surgery is multifactorial. The likelihood of developing ARF after cardiac surgery depends on the interaction of several perioperative risk factors including : old age, reduced baseline renal function, CPB duration, type of surgery and postoperative haemodynamic instability (11, 12). According to the recent evolution in cardiac surgery, we

Table V
Comparisons of ICU stay and ICU mortality
between the 3 groups

	«GEL-group» n = 1276	«MIX-group» n = 1008	«HES-group» n = 840	
ICU stay (day)	4.1 ± 5.2	5.5 ± 10.4	4.5 ± 9.2	ANOVA P < 0.005
	p < 0.005		p < 0.05	
	NS			
ICU mortality (%)	5.8	5.8	6.0	Pearson Chi-Square ; NS

observed an increase of two risk factors over the time : old age and proportion of valvular operations. These changes might be responsible for a somewhat increased renal risk and thereby could explain the non significant increase in the rates of postoperative ARF and need for postoperative dialysis observed in the MIX and HES groups gathered during the more recent periods of the study.

Acute renal failure and need for postoperative dialysis are strongly and independently associated with an increase in postoperative morbidity and mortality in cardiac surgery patients (10). Therefore, clinical interventions aimed at preventing ARF and improving renal outcome in these patients are clearly needed. However, in the absence of specific therapies to prevent ARF, clinical interventions mainly rely on clinical strategies aimed to reduce the renal risk. Among these strategies, maintaining an adequate circulating blood volume, providing haemodynamic stability and thereby optimizing renal perfusion are extremely important. Any additional nephrotoxic effect should obviously be avoided.

While non protein colloids as HES seem to be particularly attractive solutions for fluid therapy, recent studies suggested an adverse effect of HES-solutions on renal function.

Hydroxyethylstarches are polydisperse solutions of polyglucose chains. The main characteristics of HES are the mean molecular weight (Mw), the degree of molar substitution (DS) by hydroxyethyl residues and the C₂/C₆ ratio (the substitution pattern at the level of the glucose units carbon atoms). In vivo Mw differs from in vitro Mw because of hydrolysis by serum α -amylase. The rate of hydrolysis varies according to the molecular properties of the preparations. Eventually, all HES-preparations are excreted renally by glomerular filtration either directly for low Mw molecules or for big molecules after hydrolysis by serum α -amylase. In interpreting the results of various clinical

studies, it is extremely important to realize that plasma concentration over time, oncotic plasma expander effect and possible side-effects depend on the molecular properties and therefore are different for the various HES-preparations (4, 5, 6, 14).

Two main hypothesis have been proposed to explain the mechanisms of ARF associated with HES use : the induction of osmotic nephrosis-like lesions and an hyperoncotic phenomenon. Osmotic nephrosis-like lesions are not specific of HES-solutions but have been reported with many colloids. However, no univocal relationship has been found between the administration of HES, the occurrence of osmotic nephrosis-like lesions and ARF, suggesting that a multifactorial rather than a specific pathophysiological mechanism is responsible for renal dysfunction (6). Although gelatin-use has never been reported to be specifically associated with ARF, making this preparation a suitable reference solution in term of renal innocuity, it's important to emphasize that all colloids, including hyperoncotic albumin can induce ARF by raising the plasma colloid osmotic pressure, thereby reducing the glomerular filtration. This condition has been termed "hyperoncotic acute renal failure". Hyperoncotic-ARF is more likely to occur with high in vivo Mw HES with high DS. Indeed, these solutions are more prone to plasma and tissue (skin, liver, ...) accumulation. Moreover, the risk of developing hyperoncotic ARF clearly depends on the degree of hydration of the patient. The dehydrated patient with restricted crystalloid intake and receiving considerable amounts of long lasting colloids is particularly at risk.

Concerns about the deleterious renal effects of HES-solutions are mainly due to the reports of two major prospective randomized trials. In Cittanova's study, HES 200 kD, 0.6-0.66 DS (Elohes®) administered to brain-dead organ donors has been shown to worsen the early renal graft function in the recipients (7). However, a large multicentre

retrospective study failed to detect any increase in the rate of delayed graft function associated with the use of HES 200 kD, 0.5 DS in brain-dead donors (9).

In patients with severe sepsis or septic shock treated with HES or gelatin, the use of 6% HES 200 kD, 0.6-0.66 DS (Elohes®) has been shown to be an independent risk factor for ARF (8). However, several comments are to be made. Baseline serum creatinine concentrations were clearly different in the two groups: 143 µmol/l (HES) vs 114 µmol/l (gelatin). Moreover, the higher frequency of urinary sodium retention in the HES treated group suggests that HES was administered in a group of patients more severely dehydrated leading to a hyperoncotic state resulting in further renal compromise. Eventually, similar numbers of patients required renal replacement therapy in the two groups: 13/65 in the HES-group vs 11/64 in the gelatin-group; ICU mortality and median length of stay were not different in the two groups.

Other studies performed in high risk patients in various clinical setting failed to detect a deleterious effect of HES on renal function (15, 16, 17). No large scale study specifically dedicated at the analysis of the renal effect of HES in the cardiac surgery setting was available so far. However, it has been shown that third generation HES-solution with low Mw (130 kD) and low DS (0.4) did not result in deterioration of renal function (in comparison with gelatin) in a small number of elderly patients undergoing cardiac surgery (16).

So far, only the use of the slow degradable HES with high DS, Elohes®, has been consistently associated with deterioration of renal function in high risk patients. Even with this particular formulation, the studies reporting deleterious effects on renal function are not without flaws. Contrary to this, the use of HES 200 kD, 0.5 DS has never been reported to be associated with an increased risk of ARF. With the new starch preparation, 6% HES 130 kD, 0.4 DS (Voluven®) developed to improve pharmacokinetics while conserving the volume effect of HES 200 kD, 0.5 DS, further improvements in safety profile may be expected. Indeed, a single dose administration of 6% HES 130 kD, 0.4 DS did not result in any deterioration in creatinine clearance in 19 patients with non anuric renal dysfunction (creatinine clearance ranging from 15 to 108 ml/min/1.73 m²) (18).

In our study, the perioperative use of HES 200 kD, 0.5 DS to the maximum amount of 33 ml/kg did not result in alteration of renal func-

tion in cardiac surgery patients in whom continuous intravenous intake of crystalloid (≥ 40 ml/h) was provided. The only significant modification was a decrease in urinary output in the HES-group during the third period. However, the mean value of urinary output remained rather high, 2608 ± 1084 ml/d, thereby minimizing the clinical significance of this statistical finding. Taking into account the multifactorial influence of postoperative diuresis, it remains difficult to speculate about a specific cause for this somewhat decreased urinary output.

The main interest of the present study was to provide a large scale analysis of the impact of HES-solution on renal function in cardiac surgery patients, a group of patients particularly at risk for postoperative renal dysfunction because of multiple risk factors. Such data were not available in literature so far. Our study, however, has several limitations. First, it is not a randomized controlled trial; the data were collected during three consecutive time periods. However, cohort data bases provide sample sizes that usually cannot be achieved in the clinical trial setting. Moreover, the inclusion of consecutive patients avoids the enrollment bias that may be present in prospective trials. It has been suggested that cohort studies may be more representative for routine clinical practice. Data completion rate in the present study was 100%.

The alleged negative effects of HES were assessed against gelatin a well accepted reference in term of renal safety. The clinical management was formally stereotyped and followed strict protocols. Although no randomization was performed in this retrospective study, cardiac surgery patients constitute a rather homogeneous population; a descriptive analysis of the risk factors per treatment group was performed. Several unbalances in renal risk factors were detected between the three groups (ie: old age, proportion of valvular operations); however because these differences were in favour of the gelatin-group, it is unlikely they could affect the validity of the conclusion. Indeed, these unbalances should have resulted in magnifying rather than obscuring the possible nephrotoxic effects of HES. However, because of the duration and the nature of the study, we cannot exclude that unrecognized changes in other risk factors may have had a significant impact on postoperative renal function.

In conclusion, the use of HES 200 kD, 0.5 DS as volume expander in addition to crystalloid intake in cardiac surgery patients does not seem to be associated with a clinically significant deterioration of postoperative renal function.

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