CURRENT OPINION

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Hydroxyethylstarch as a Risk Factor for Acute Renal Failure

Is a Change of Clinical Practice Indicated?

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Abstract

Hypovolaemia is extremely common among surgical and intensive care patients. The best strategy for volume replacement therapy has been the focus of debate for several years. The lack of acceptance of hydroxyethylstarch (HES) for volume replacement therapy is most likely due to reports of abnormal coagulation and to recently published studies indicating negative effects of HES on renal function. All HES solutions are not created equal – they widely differ with regard to their physicochemical characteristics (concentration, mean molecular weight (Mw), degree of substitution [DS], C2/C6-substitution ratio). These differences have important consequences for adverse effects such as alterations in the coagulation process and on kidney function. Conflicting results about the effects of different HES solutions on renal function may also be due to varying clinical protocols, selection of patients, and different criteria for volume replacement. Theoretical and documented hazards are associated with each kind of volume replacement therapy. There appears to be no reason to banish modern HES preparations with a low or medium Mw (e.g. 70, 130 or 200kD) and a low DS (0.4 or 0.5) in patients without pre-existing kidney dysfunction. In patients with known renal dysfunction (e.g. plasma creatinine level >3 mg/dl), all HES preparations should be used cautiously and other volume replacement regimens (e.g. gelatins) should be considered since no convincing data are yet available for the latest generation of HES (Mw 130; DS 0.4).

Adequate volume replacement is an important therapeutic manoeuvre in managing the critically ill patient. Absolute or relative blood volume deficits often occur in the critically ill. Bleeding may cause absolute volume deficits and vasodilation mediated by vasodilating substances (e.g. anaesthetics, nitroglycerin) is also involved in producing relative volume deficits. Volume deficits can also develop in the absence of obvious fluid loss secondary to generalised altered endothelial barrier resulting in diffuse 'capillary leak' (e.g. during inflammation or sepsis).

Hypovolaemia may be associated with flow alterations that are inadequate to fulfil the nutritive role of the circulation. During hypovolaemia-related haemodynamic dysfunction the body tries to compensate perfusion deficits by redistribution of flow to vital organs (e.g. heart, brain) resulting in an underperfusion of other organs such as gut, kidneys, muscles, and skin. Activation of the sympathetic

nervous system and the renin-aldosterone-angiotensin system are compensatory mechanisms to maintain peripheral perfusion. Various circulating vasoactive substances and inflammatory mediators are additionally released in this situation. Although this compensatory neurohumoral activation is beneficial at first, this mechanism becomes deleterious and may be involved in poor outcomes in hypovolaemic patients. In a prospective review of 111 consecutive patients who died in hospital after admission for treatment of injuries, the most common defects in the management of these patients were related to inadequate fluid resuscitation.[1] Thus, an adequate volume replacement therapy may help to improve organ function and reduce the morbidity or even mortality of such patients.

Blood and blood component therapy should be restricted to those patients presenting with severe anaemia or coagulation disorders. Non-blood alternatives for volume replacement have to be defined. The choice between colloid and crystalloid solutions continues to generate controversy. The crystalloid-colloid dispute has been enlarged to a colloid-colloid debate because aside from the natural colloid albumin several synthetic colloids are available as plasma substitutes.[2] Hydroxyethylstarch (HES) is widely used because it is a cheap alternative to albumin and because of its excellent volume replacement efficacy. However, development of renal dysfunction is one of the problems with the use of HES that have been reported as an important reason for avoiding use of this substance.[2-6]

1. How is Renal Function Altered in the Critically Ill?

An abrupt decline in renal function, e.g. a sudden and sustained decline in the glomerular filtration rate (GFR), is defined as acute renal failure (ARF). The factors initiating ARF are classified as either prerenal (inadequate perfusion, hypoxia), renal (intrinsic kidney diseases, toxins, ischaemia), or post-renal (obstructive uropathy).[7] Prerenal disease (hypotension, volume depletion, hypoxia) is the most often reason for acute renal dysfunction in surgery and intensive care.[8] The common denominator is a (reversible) decrease in glomerular capillary pressure, which in turn is a major determinant of the GFR. The control of blood flow to the kidney and to the glomerulus and tubules is autoregulated by several mechanisms. Potent mediators of the control of the pressure gradient across the glomerular membrane are catecholamines, atrial natriuretic peptide, angiotensin and prostaglandins. The interaction of these mediators is fundamental to the understanding of how urine flow is maintained. ARF induced by ischaemia or cellular toxins is characterised by modifications in glomerular haemodynamics.[9] A reduction in net transglomerular hydraulic pressure may be induced by a raise in proximal tubular pressure or a fall in the hydraulic pressure in the glomerular capillary. Additionally, glomerular permeability and tubuloglomerular feedback activation may also be associated with a reduction in GFR. Last but not least, back leakage of filtrate across a damaged tubular endothelium can further reduce renal excretory capacity.

2. Development of Acute Renal Failure: Who is at Particular Risk?

The onset of ARF could be the consequence of multifactorial aetiologies. Pre-existing kidney diseases, vascular disease, diabetes mellitus, arterial hypotension/hypertension, hypothermia, hypoxia, cardiopulmonary bypass (CPB), the kind of surgery (e.g. aortic surgery) have been considered important factors for the development of renal dysfunction.[7,8,10,11]

Haemodynamic instability due to volume depletion is one of the most important determinants for developing ARF in the critically ill. Additionally, several substances are known that *per se* may deteriorate renal function (e.g. catecholamines, aminoglycosides). After cardiac surgery, ARF occurs in 0.7 to 5% of patients.[10,12] Transient, moderate changes of renal function are reported to occur with a frequency rate of up to 30% after car-

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diac surgery using CPB.[10] Elderly patients appear to be particularly prone to developing renal dysfunction.[13,14] The most important alteration in the elderly is a decrease in GFR, as demonstrated by a decrease in creatinine clearance.[13] After the age of 40 years, creatinine clearance decreases by approximately 1% per year.[13] Moreover, the ability to compensate disturbances of renal function is limited in the elderly. Renal function deteriorates earlier, particularly secondary to application of nephrotoxic substances.[13]

3. Renal Effects of Colloidal Plasma Substitutes

All colloids including hyperoncotic albumin solutions may induce ARF by raising the plasma colloid osmotic pressure (COP).[9] This has been termed 'hyperoncotic acute renal failure'. In particular, the dehydrated patient who receives considerable amounts of hyperoncotic colloids is at risk of developing 'hyperoncotic ARF'. Thus, all colloids have to be administered in addition rather than in lieu of crystalloids.

3.1 Gelatins

Gelatins appear to be devoid of damaging effects on kidney function,[15] although acute renal failure following the infusion of gelatin has also been occasionally reported.[16]

3.2 Dextrans

In humans without kidney dysfunction, 70% of intravenously administered low-molecular weight dextran is excreted within 12 hours.[17,18] The pathogenesis of dextran-induced ARF appears to be multifactorial including 'hyperoncotic ARF', tubular obstruction, and direct toxicity. Renal biopsies or autopsies revealed proximal tubular cell swelling and vacuolisation termed 'osmotic nephrosis'. However, these 'osmotic nephrosis-like lesions' appear to be a rather unspecific phenomenon because they have been demonstrated with other substances as well (e.g. mannitol, hypertonic glucose, cyclosporin).[6] Moreover, the functional significance of these lesions is questionable. Tubular obstruction has been postulated to be another mechanism involved in the pathogenesis of ARF after dextran infusion, and clinical improvement has been shown if urine flow is elevated by diuretics.[18,19]

3.3 Hydroxyethylstarch (HES)

The substance HES is a highly polymeric glucose compound that is manufactured through hydrolysis and hydroxyethylation from the highly branched starch amylopectin (figure 1). HES preparations are characterised by: concentration; the number average molecular weight (Mn: the mass of the sample in grams divided by the total number of chains or the simple numerical average of the

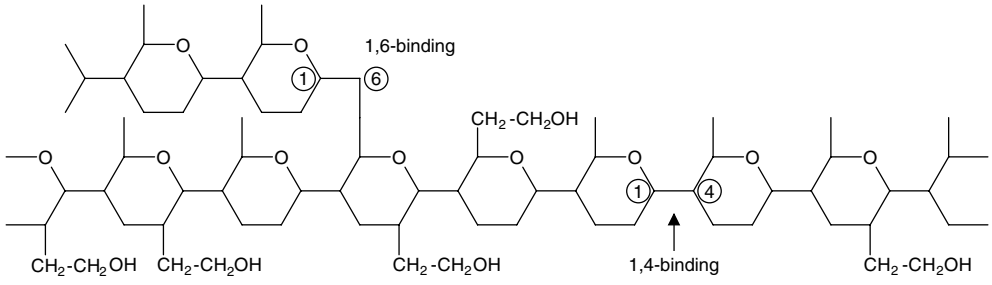

Fig. 1. Enzymatic degradation of hydroxyethylstarch via α-1,4-amylase. Degradation depends on: (i) degree of substitution (high = prolonged degradation); (ii) substitution pattern C2/C6 (high = prolonged degradation); (iii) molecular weight (only of importance when >70kD [renal threshold]).

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Table I. Physico-chemical characteristics of the different hydroxyethylstarch (HES) preparations

	HES 70/0.5	HES 130/0.4	HES 200/0.5	HES 200/0.5	HES 200/0.62	HES 450/0.7
Concentration (%)	6	6	6	10	6	6
Volume efficacy (%)	80	100	100	130-150	100	100
Volume effect (h)	Short (1-2)	Medium (2-3)	Medium (3-4)	Medium (3-4)	Long (5-6)	Long (5-6)
Mean molecular weight (Mw) [kD]	70	130	200	200	200	450
Degree of substitution (DS)	0.5	0.4	0.5	0.5	0.62	0.7
C2/C6 ratio	4 : 1	9 : 1	6 : 1	6 : 1	9 : 1	4.6 : 1

individual weights); the weight average molecular weight (mean molecular weight [Mw]: the sum of each molecule's weight divided by the total mixture's weight multiplied by the weight of the molecule); the molar substitution (MS: the molar ratio of the total number of hydroxyethyl groups to the total number of glucose units); and the degree of substitution (DS: the ratio of substituted glucose units to the total number of glucose molecules).

A huge variety of HES preparations are available in severe countries with different concentrations (3, 6 and 10%), Mw (low-molecular weight [LMW]-HES: 70 or 130kD; medium-molecular weight [MMW]-HES: 200 to 270kD dalton; high-molecular weight [HMW]-HES: 450kD), and different DS (low DS: 0.4, 0.5; high DS: 0.62, 0.7) [table I]. A substantial body of evidence supports the concept that the ratio of the C2 **:** C6 hydroxyethylation appears to be an important factor for pharmacokinetic effects and possibly also for some adverse effects (e.g. accumulation, bleeding complications).[20]

3.4 Damage of the Renal System by HES: Fact or Fiction

The pharmacokinetics of HES preparations are divided into redistribution and renal excretion. The elimination of HES molecules varies widely with Mw and, most importantly, with the DS. Subsequently it is essential to distinguish the different HES preparations ('all colloids are not created equal'[21]). Large HES molecules are split by hydrolytic cleavage by α-amylase, whereas the smaller HES molecules are eliminated by glomerular filtration (figure 1). The higher the DS (e.g. 0.62 or 0.7), the slower the breakdown and elimination of the molecule (figure 2) and the more pronounced the effects on plasma viscosity (table II). Molecules <50kD are rapidly filtered by the kidneys, larger molecules are hydrolysed by α-amylase and excreted in urine or phagocytosed by the reticuloendothelial system Some toxicological studies have shown reversible swelling of tubular cells of the kidneys after administration of HES preparations, which appears to be most likely due to reabsorption of macromolecules.[22] Swelling in tubular cells causes tubular obstruction and medullar ischaemia, two important risk factors for the development of ARF.[23] Glomerular filtration of hyperoncotic molecules causes a hyperviscose urine and a stasis of tubular flow resulting in obstruction of tubular lumen.[24] The effective glomerular filtration pressure (Peff) is (equation 1):

$$(Pcap - Pbow) - Ppla$$

where Pcap = hydrostatic capillary pressure; Pbow = hydrostatic pressure in Bowman space; and Ppla = plasma colloid osmotic pressure.

An increase of COP by hyperoncotic colloids may be one reason for renal dysfunction[30,31] (figure 3). Thus, use of considerable amounts of colloids in 'dry' patients must be avoided. The mechanism as to how HES may directly alter kidney function is not definitely known. There appears to

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be no relation between evidence of 'osmotic nephrosis-like lesions' and kidney function after administration of HES (e.g. incidence of renal replacement therapies).[32]

4. What Does the Literature Tells Us About Renal Function and HES

There is evidence from some literature reports that patients infused with HES may experience altered kidney function.[3-5,32,33] Unfortunately, our current understanding of this area is poor. Thus, for a more systematic analysis of this problem, studies dealing with volume replacement therapy with HES and renal function were searched using a Medline analysis (tables III and IV). Only English-language original research articles published in the period from 1981 to 2001 were analysed and included. Experimental or animal studies and reviews were not analysed. Only studies comparing different volume replacement regimens with regard to renal function were included because it appears not to be feasible to compare a volume infusion group with a control group of patients in whom no volume was administered.

Twelve studies that fulfilled the criteria were identified.[3,5,15,32,34-41] A retrospective study analysis of patients who underwent kidney transplantation and in whom HES with a high DS (0.62) was infused was the first report showing adverse effects of a HES preparation on kidney function.[32] Only the HES-treated group showed 'osmotic nephrosis-like lesions', but no negative effects on graft function or serum creatinine, 3 and 6 months after transplantation were seen. A similar group of patients were prospectively studied by Cittanova et al.[3] Infusion of 2100 ± 660ml of 6% HES 200/0.62 in donors who were brain-dead resulted in deteriorated renal function in kidney transplant recipients. Patients who received kidneys from HES-treated donors showed higher serum creatinine concentrations and a more frequent incidence of haemodialysis compared with patients who received kidneys from gelatin-treated donors. Interestingly, another retrospective study with the same kind of patients could not demonstrate any negative effects on kidney function when 6% HES 450/0.7 or 6% HES 200/0.5 were compared with a group of donors treated with gelatin/albumin.[39]

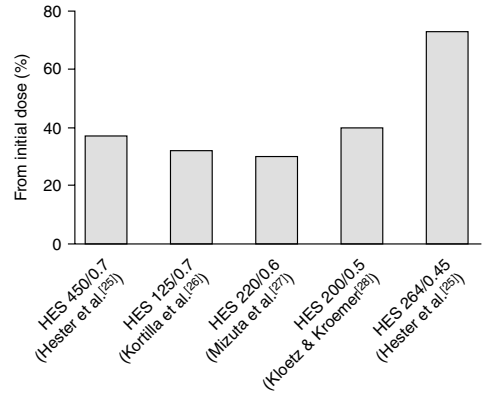

Fig. 2. Urinary elimination of different hydroxyethylstarch (HES) preparations in 24 hours (mean molecular weight/degree of substitution).[29]

4.1 Perioperative Use

The influence on perioperative volume replacement therapy on renal function was shown only in six studies.[15,34,35,37,40,41] In two of the studies car-

Table II. Effects of different hydroxyethystarch preparations on plasma viscosity

In vitro Mw	Substitution	C2/C6 ratio	*In vivo* Mw	Plasma viscosity (%)	p-Value
40	0.5	3	57.5	–1.5	NS
200	0.5	6	84.1	+3.1	NS
200	0.5	13	95.0	+10.1	<0.01
200	0.62	10	120.6	+18.5	<0.01

Mw = mean molecular weight; **NS** = not significant.

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diac surgery patients, who are at particular risk of developing postoperative renal dysfunction, were included.[34,40] In both of these studies, HES with a medium Mw and a low DS were infused. Renal function remained unchanged by HES administration. In patients without altered renal function undergoing middle ear surgery,[41] low doses (15 ml/kg) of different HES preparations (6% HES 450/0.7, 6% HES 200/0.62 or 6% HES 200/0.5) did not result in disturbed renal function as assessed by several markers of altered renal integrity (e.g. α_1-microglobulin, *N*-acetyl-beta-glucosaminidase [NAG], Tamm-Horsfall-protein, inulin clearance). In elderly (>65 years) and younger patients (<65 years) without preoperative renal dysfunction undergoing major abdominal surgery, the influence of different intravascular volume replacement regimen on renal function was assessed in a prospective, randomised study.[37] Either LMW-HES (Mw 70kD, DS 0.5), MMW-HES (Mw 200kD, DS 0.5) or modified gelatin (Mw 35kD) were administered to keep mean arterial blood pressure (MAP) >65mm Hg and central venous pressure (CVP) between 10 to 14mm Hg. Up to the first postoperative day, 1300 to 3000ml of colloids were infused. The intravascular volume therapy with gelatin and the two HES preparations did not adversely affect renal function in elderly surgical patients without preoperative renal malfunction. Aside from creatinine clearance, more sensitive markers of renal dysfunction were also measured in this study. By measuring these kidney-specific proteins, alterations in kidney integrity can be assessed in the absence of modified creatinine clearance. For example, α_1-microglobulin is a low molecular weight tubular protein which can be used for diagnosing

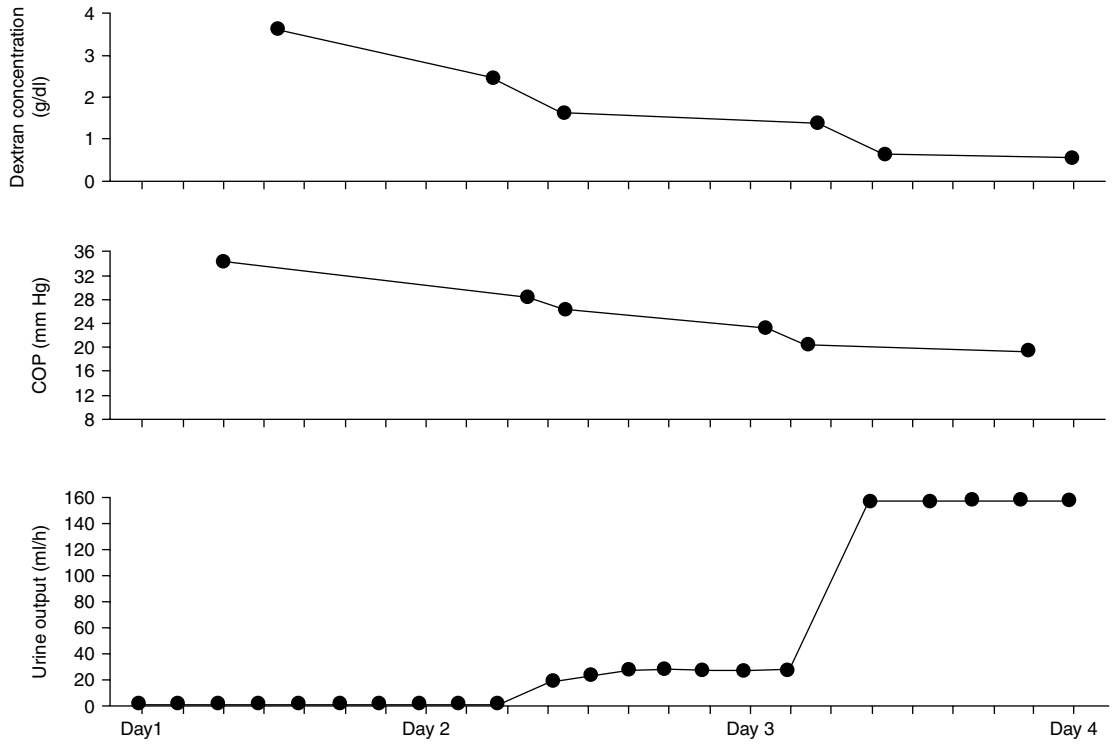

Fig. 3. Influence of increased colloid oncotic pressure (COP) on renal function.[9]

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Table III. Studies of volume replacement with hydroxyethylstarch (HES) showing altered renal function with HES

Study	HES preparation (no. of patients)	Comparator (no. of patients)	Study design	Patient group	Aim	Renal function prior study	Conclusion
Legendre et al.[32]	6% HES 200/0.62 (39)	NS	Retrospective	Brainstem dead patients; kidney transplant recipients	Not defined	NS	More 'osmotic nephrosis-like lesions' with HES but no increase in kidney dysfunction (as measured by creatinine levels)
Cittanova et al.[3]	6% HES 200/0.62 (15)	Gelatin (12)	Prospective, randomised	Brain-dead kidney donors	Not defined	Not known	Higher creatinine levels were seen with patients receiving HES and the frequency of renal failure was greater. Mortality rate did not differ
Schortgen et al.[5]	6% HES 200/0.62 (65)	Gelatin (64)	Prospective, randomised, multicentre	Sepsis/septic shock; ICU	Fixed dose	Elevated creatinine levels	Creatinine clearance and the incidence of ARF was higher with HES. Mortality rate did not differ

ARF = acute renal failure; **ICU** = intensive care unit; **NS** = not stated.

tubular damage. It is freely filtered at the glomerulus and normally reabsorbed by the renal tubule. Increased urine concentrations of α_1-microglobulin therefore reflect failure of tubular reabsorption function. It is a sensitive marker for the early phase of renal failure. NAG is a lysosomal enzyme present mainly in the proximal tubular cells. It is a large molecular weight enzyme secreted by tubular cells, and reflects increased tubular turnover of reabsorbed substances. An increase in NAG leakage into urine has been shown in the presence of tubular lesions and is another early marker for detecting renal failure.

4.2 Use in the Intensive Care Unit

In four studies intensive care unit (ICU) patients were included.[5,34,36,38] In three of them, use of human albumin was compared with HES.[34,36,38] In only one study was significant alterations in kidney function with a HES preparation shown.[5] In this multicentre study, 129 patients with sepsis or septic shock received either gelatin (3% fluid-modified gelatin; n = 64) or a HES preparation (Mw 200kD, DS 0.62, n = 65) for volume replacement therapy. Median cumulative volume replacement was 31 ml/kg with HES and 43 ml/kg with gelatin. Acute renal failure (defined as a 2-fold increase in serum creatinine level or need for renal replacement therapy) developed in 27% of the HES-treated patients (42%) and in 15 of the gelatin-infused patients (23%) [$p < 0.028$]. Differences in creatinine levels became significantly different 6 days after first use of HES. Unfortunately, the two treatment groups had different creatinine levels prior to the start of volume therapy: median serum creatinine levels were 143 and 114 μmol/L, in the HES- and gelatin-treated patients, respectively. Compared with the gelatin-group, use of the slow degradable HES preparation (HES 200/0.62) was an independent risk factor for the occurrence of ARF. In spite of a higher incidence of ARF (increased incidence of haemodialysis) in the HES 200/0.62-treated patients, mortality was not significantly different between the two groups.

4.3 Influence of Repetitive Doses of HES on Renal Function

There are only limited data available on the influence of repetitive doses of HES on kidney function. In one study, use of HES 200/0.5 over 5 days

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Table IV. Studies on volume replacement with hydroxyethylstarch (HES) showing no alteration in renal function

Study	HES preparation (no. of patients)	Comparator (no. of patients)	Study design	Patient group	Aim	Renal function (prior study)	Conclusion
London et al.[34]	10% HES 260/0.45 (50)	5% HA (44)	Prospective, randomised	ICU and after cardiac surgery	Maintain CI >2.0 L/min/m^2	Normal kidney function	Creatinine + urine output: no differences between treatment groups. Outcome: no differences between treatment groups
Vogt et al.[35]	6% HES 200/0.5 (20)	5% Albumin (21)	Prospective, randomised	Total hip arthroplasty	Replace blood loss	Normal kidney function	No differences between treatment groups in renal function, even after high dose. Outcome: NS
Beyer et al.[15]	6% HES 200/0.5 (19)	Gelatin (22)	Prospective, randomised	Orthopaedic surgery patients	According to haemodynamics function	Normal kidney outcome: not shown	No differences between treatment groups in serum creatinine levels and urine output
Boldt et al.[36]	10% HES 200/0.5 (150)	20% HA (150)	Prospective, randomised	ICU patients trauma sepsis	PCWP 12-15mm Hg	Normal creatinine: 1.0-1.9 mg/dl	No differences between treatment groups in serum creatinine levels and urine output
Kumle et al.[37]	6% HES 70/0.5 (20); 6% HES 200/0.5 (20)	Gelatin (20)	Prospective, randomised	Major abdominal surgery	CVP 10-14mm Hg	Normal kidney function	No differences between treatment groups in renal function and outcome
Allison et al.[38]	6% HES 250/0.45 (24)	Gelatin (21)	Prospective, randomised	Trauma patients ICU	Not defined	Not known	No differences between treatment groups in serum creatinine levels and urine output. Outcome: NS
Deman et al.[39]	6% HES 200/0.5 (20); 6% HES 450/0.7 (16)	Gelatin/albumin (73)	Retrospective cohort study	Brain-dead kidney donors	Not defined	Not known	Higher serum creatinine levels with HES 450/0.7. No difference between treatment groups for ARF. Outcome: NS
Boldt et al.[40]	6% HES 130/0.4 (10); 6% HES 200/0.5 (10)	No comparator	Prospective, randomised, double-blind	Cardiac surgery patients	Fixed dose 10 ml/kg	Normal kidney function	No differences between treatment groups in serum creatinine levels, urine output or outcome
Dehne et al.[41]	6% HES 200/0.5 (15); 6% HES 200/0.62 (15); 6% HES 450/0.7 (15)	RL (15)	Prospective, randomised	Middle-ear surgery	Fixed dose HES: 15 ml/kg; RL: 60 ml/kg	Normal kidney function	No negative effects on kidney function with HES. Outcome: no differences between treatment groups

ARF = acute renal failure; **CI** = cardiac index; **CVP** = central venous pressure; **HA** = human albumin; **ICU** = intensive care unit; **NS** = not stated; **PCWP** = pulmonary capilliary wedge pressure; **RL** = Ringer's lactate.

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in ICU patients was without negative effects on renal function (serum creatinine, urine output, need for haemofiltration) compared with a control group in whom human albumin was administered.[36]

4.4 Influence of the Amount of HES on Renal Function

Whether the amount of HES used is of importance when looking at deterioration in kidney function in HES-treated patients is unknown. In a study by Schortgen et al.,[5] involving patients with sepsis/septic shock, ARF occurred although less HES 200/0.62 (median dose: 31 ml/kg) than that recommended by the manufacturer (33 ml/kg) was given. In a case report of a patient undergoing buccopharyngectomy, even a very small dose of HES 200/0.5 (500ml [<10 ml/kg]) was suspected of causing ARF.[4] Unfortunately, in several studies the absolute amount of the administered solution was not mentioned. High-volume therapy was used in one study in orthopaedic patients:[35] even about 3000ml of a modern HES preparation (HES 200/0.5) did not alter kidney function compared with a 5% human albumin-based volume replacement regimen.

5. Conclusions

The choice of agent for fluid replacement therapy engenders controversy and an examination of the body of literature on this subject results in confusion. It has been questioned whether meta-analyses are helpful in examining the effects of the type of volume replacement strategy on mortality,[42] because mortality is not an end-point of any of the crystalloid-colloid studies. Moreover, mortality does not seem to be an appropriate end-point when comparing different volume replacement regimens. Effects of different fluids should be focused on organ function (kidneys), inflammation, or perfusion.[42]

HES has been used for treatment of volume deficits for several years. The lack of information on its influence on kidney function is astonishing. Against this background, it is surprising to be confronted with statements like 'renal toxicity of HES is now well recognised',[6] or that administration of even low doses of HES causes tubular lesions in patients predisposed to renal insufficiency.[4]

It has been established as general practice to use HES in patients with a plasma creatinine level >3.0 mg/dl very cautiously and to favour use of other colloids (e.g. gelatin) or crystalloids in these patients. However, a substantial body of evidence supports the concept that the different HES specifications must be distinguished[9,21] and this is also true for the effects on kidney function. In patients without pre-existing renal dysfunction, modern HES solutions (HES 70/0.5; HES 200/0.5, HES 130/0.4) can be safely used with regard to kidney function. This, however, is no carte blanche in patients with existing kidney function alterations. All colloids (including HES) have to be administered in addition to rather than in lieu of crystalloids (e.g. in a 2 : 1 or 3 : 1 ratio). As they are not rapidly degradable, HES preparations (with a high DS [0.62; 0.7]) should be avoided in patients who are at elevated risk of developing ARF (e.g. in cardiac surgery, in the intensive care patient). It is imperative to continue the search for pharmacological agents that are without detrimental adverse effects. Whether the most recently developed HES preparation (HES 130/0.4) is a new 'high-light' in treating volume deficits in patients with pre-existing deteriorated renal function, remains to be elucidated.

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References

1. Deane SA, Gaudry PL, Woods P, et al. The management of injuries – a review of death in hospital. Aust N Z J Surg 1988; 58: 463-9
2. Edwards JD. A new debate: colloid versus colloid?. In: Vincent JL, editor. Yearbook of Intensive Care and Emergency Medicine. Berlin, Heidelberg, New York: Springer, 1994: 152-64

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3. Cittanova ML, Leblanc I, Legendre Ch, et al. Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. Lancet 1996; 348: 1620-2
4. De Labarthe A, Jacobs F, Blot F, et al. Acute renal failure secondary to hydroxyethylstarch administration in a surgical patient. Am J Med 2001; 111: 417-8
5. Schortgen F, Lacherade JC, Bruneel F, et al. Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicenter randomised study. Lancet 2001; 357: 911-6
6. Peron S, Mouthon L, Guettier C, et al. Hydroxyethyl starch-induced renal insufficiency after plasma exchange in a patient with polymyositis and liver cirrhosis. Clin Nephrol 2001; 55: 408-11
7. Byrick RJ, Rose DK. Review article: pathophysiology and prevention of acute renal failure: the role of the anaesthetist. Can J Anaesth 1990; 37: 457-67
8. Rahn KH. Acute disturbances of renal function. Chest 1991; 100: 197S-9S
9. Moran M, Kapsner C. Acute renal failure associated with elevated plasma oncotic pressure. N Engl J Med 1987; 317: 150-3
10. Kulka PJ, Tryba M, Zenz M. Preoperative alpha-2-adrenergic receptor agonists prevent the deterioration of renal function after cardiac surgery: results of a randomized, controlled trial. Crit Care Med 1996; 24: 947-52
11. Lote CJ, Harper L, Savage COS. Mechanisms of acute renal failure. Br J Anaesth 1996; 77: 82-9
12. Aronson S, Blumenthal R. Perioperative renal dysfunction and cardiovascular anesthesia: concerns and controversies. J Cardiothorac Vasc Anesth 1998; 12: 567-86
13. Lindeman RD. Changes in renal function with aging: Implications for treatment. Drugs Aging 1992; 2: 423-31
14. Ritschel WA. Gerontokinetics: the pharmacokinetics of drugs in the elderly patient. Caldwell (NJ): Telford Press, 1988: 114-24
15. Beyer R, Harmening U, Rittmeyer O, et al. Use of modified fluid gelatin and hydroxyethyl starch for colloidal volume replacement in major orthopaedic surgery. Br J Anaesth 1997; 78: 44-50
16. Hussain SF, Drew PJT. Acute renal failure after infusion of gelatins. BMJ 1989; 299: 1137-8
17. Kurnik BRC, Singer F, Groh WC. Case report: dextran-induced acute renal failure. Am J Med Sci 1991; 302: 28-30
18. Figueroa JE, Burgos-Calderon R. Renal toxicity of low molecular weight dextran: a review of the literature. J La State Med Soc 1974; 126: 425-7
19. Feest TG. Low molecular weight dextran: a continuing cause of acute renal failure. BMJ 1976; 2: 1300-1
20. Treib J, Haass A, Pindur G, et al. HES 200/0.5 is not HES 200/0.5 – influence of the C2/C6 hydroxyethylation ratio of hydroxyethyl starch (HES) on hemorheology, coagulation and elimination kinetics. Thromb Haemost 1995; 74: 1452-6
21. Traylor RJ, Pearl R. Crystalloid versus colloid: all colloids are not created equal. Anesth Analg 1996; 83: 209-12
22. Kief H, Engelhart K. Reabsorptive Vacuolisation der gewundenen Nierenhauptstücke (sog. osmotische Nephrose). Frank Zeitschr für Path 1966; 75: 53-9
23. Iana A, Schwartz D. Renal tubular cellular and molecular events in acute renal failure. Nephron 1994; 68: 413-8
24. Chinitz JL, Kim KE, Onesti G, et al. Pathophysiology and prevention of dextran-40-induced anuria. J Lab Clin Med 1971; 77: 76-87
25. Hester J, McEntegrat C, Hulse JD, et al. Clinical study no. 607-85-09. Rockville (MD); Dupont
26. Kortilla K, Grohn P, Gordin A, et al. Effects of hydroxyethyl starch and dextran on plasma volume and blood hemostasis and blood coagulation. J Clin Pharmacol 1984; 24: 273-82
27. Mizuta S, Ikeda K, Iguchi K. Clinical study with hydroxyethly starch 200/0.6: hemodynamic data, metabolism and elimination. Med Consult New Remedies 1971: 8: 2493-2500
28. Kloetz U, Kroemer U. Clinical pharmacokinetic considerations in the use of plaxma volume expanders. Clin Pharmacokinet 1987; 12: 123-35
29. Baron JF. Clinical use of hydroxyethyl starches. In: Vincent JL, editor. Update in intensive care and emergency medicine. Vol. 14. New York (NY); Springer, 1991: 403-14
30. Druml W, Pölzleitner D, Laggner AN, et al. Dextran-40, acute renal failure, and elevated plasma oncotic pressure. N Engl J Med 1988; 318: 252-3
31. Rozich JD, Paul RV. Acute renal failure precipitated by elevated colloid osmotic pressure. Am J Med 1989; 87: 358-60
32. Legendre C, Thervet E, Page B, et al. Hydroxyethylstarch and osmotic-nephrosis-like lesions in kidney transplantation. Lancet 1993; 342: 248-9
33. Coronel B, Mercatello A, Martin X, et al. Hydroxyethylstarch and renal function in kidney transplant recipients. Lancet 1997; 349: 884
34. London MJ, Ho SJ, Triedman JK, et al. A randomized clinical trial of 10% pentastarch (low molecular weight hydroxyethyl starch) versus 5% albumin for plasma volume expansion after cardiac operations. J Thorac Cardiovasc Surg 1989; 97: 785-97
35. Vogt NH, Bothner U, Lerch G, et al. Large-dose administration of 6% hydroxyethyl starch 200/0.5 for total hip arthroplasty: plasma homeostasis, hemostasis, and renal function compared to use of 5% human albumin. Anesth Analg 1996; 83: 262-8
36. Boldt J, Müller M, Mentges D, et al. Volume therapy in the critically ill: is there a difference? Intensive Care Med 1998; 24: 28-36
37. Kumle B, Boldt J, Piper SN, et al. The influence of different intravascular volume replacement regimens on renal function in the elderly. Anesth Analg 1999; 89: 1124-30
38. Allison KP, Gosling P, Jones S, et al. Randomized trial of hydroxyethyl starch versus gelatine for trauma resuscitation. J Trauma 1999; 47: 1114-21
39. Deman A, Peeters P, Sennesael J. Hydroxyethyl starch does not impair immediate renal function in kidney transplant recipients: a retrospective, multicenter analysis. Nephrol Dial Transplant 1999; 14: 1517-20
40. Boldt J, Lehmann A, Römpert R, et al. Volume therapy with a new hydroxyethyl starch solution in cardiac surgical patients before cardiopulmonary. J Cardiothorac Vasc Anesth 2000; 14: 264-8
41. Dehne MG, Mühling J, Sablotzki A, et al. Hydroxyethylstarch (HES) does not directly affect renal function in patients with no prior renal impairment. J Clin Anesth 2001; 13: 103-11
42. Astiz ME, Rackow EC. Crystalloid-colloid controversy revisited. Crit Care Med 1999; 27: 34-5

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