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INVITED REVIEW ARTICLE

Kidney function after the intraoperative use of 6 % tetrastarches (HES 130/0.4 and 0.42)

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Abstract Concerns about the nephrotoxicity of tetrastarches have recently increased with the accumulation of new evidence, particularly in relationship to septic patients. Two meta-analyses in 2011 and early 2012 also raised concerns about nephrotoxicity in surgical patients and prompted the present review of the nephrotoxicity of tetrastarches solely in the surgical setting. Seven reports consisting of two review articles and five single-trial papers published between 2012 and August 2013 were examined. Six of the seven studies did not show any adverse renal outcomes following the intraoperative use of tetrastarch, although their data are not robust enough to confirm definitive safety. Moreover, balanced electrolyte solutions are strongly recommended as a carrier solution for tetrastarches to reduce adverse outcomes.

Keywords Hydroxyethyl starch · Kidney function · Surgery · Safety

Introduction

Synthetic colloids generally have an advantage over crystalloids regarding their effect on intravascular volume expansion. However, synthetic colloids are potentially harmful, as reflected in their dose-related side effects including renal impairment, increased bleeding tendency, and tissue accumulation with organ damage [1]. Among the synthetic colloids, hydroxyethyl starch (HES) has been widely used in intensive care and surgical settings. A potential risk of nephrotoxicity following the use of HES has recently emerged, even with modern third-generation HES (tetrastarch), in intensive care patients and especially septic patients [2–6]. It is also suggested that tetrastarch is not convincingly safe in surgical patients, even though tetrastarch was considered safe without serious nephrotoxicity until recently [7, 8]. However, even in review articles on perioperative kidney injury published as late as 2013 tetrastarch has not been recognized as a nephrotoxic drug [9, 10]. Furthermore, there has been no update on the differential effects of resuscitation with colloids in septic shock and hypovolemic shock since Hogan's report [11] around 100 years ago, which stated that resuscitation with colloids is more effective than normal saline (0.9 % NaCl) in hypovolemic shock but is insufficient in septic shock.

In this context, reports focusing solely on the surgical setting would be helpful in examining this issue in more detail, because tetrastarch may be administered for shorter periods at lower doses in surgical patients than in intensive care patients. Also, because the several articles on tetrastarch published in 2012 and 2013 were not included in previous review articles [7, 8], the present review was undertaken to provide an update on the nephrotoxicity of tetrastarch solely in the surgical setting.

Tetrastarch: third-generation HES

During the past few decades, HES products have been improved to reduce adverse effects by decreasing their concentration, mean molecular weight, and/or molar substitution of starch molecules while maintaining efficacy. According to a review article by Westphal et al. [12] clearance of tetrastarch is at least 23 times higher than that of hexastarch, and tetrastarch improves tissue oxygenation

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Table 1 Chracteristics of third-generation hydroxyethyl starch (tetrastarch)

	HES 130/0.4	HES 130/0.42
Raw material	Waxy maize	Potato
Year of synthesis	1957	1994
HES concentration	6 %, iso-oncotic	6 %, iso-oncotic
Mean molecular weight (kDa)	130	130
Molar substitution[a]	0.41	0.45–0.46
C_2:C_6 ratio[a]	9:1	6:1
Content of amylopectin (%)[b]	98	75
Maximum daily dose (ml/kg)[c]	50	50

Source: Westphal et al. [12]; Ertmer et al. [41]

[a] A higher value indicates a slower degradation or elimination of starch polymer by amylase

[b] A higher value indicates a lower viscosity

[c] Based on ideal body weight according to the manufacturer's recommendation

compared with a crystalloid-based volume strategy. Until a few years ago, tetrastarches (Table 1) were believed to have no adverse effects, except in patients with prior mild to severe renal dysfunction, elderly patients, and patients who received a large HES dose [12]. However, the paucity of evidence supporting the safety of tetrastarch in both surgical and intensive care patients has become evident in recent years [7, 8].

Pathological mechanism of HES-induced nephrotoxicity

Concerns about the possible adverse renal effects of HES were first raised by Legendre et al. [13]. However, the pathological mechanism of HES-induced nephrotoxicity has not been well understood; it cannot be determined whether oncotic force, molecular weight, degree of molar substitution, molecular size, colloid carrier solution, or a combination of these factors is responsible for the HES-induced nephrotoxicity [14]. Additionally, the effect and safety of HES seems to be different when HES is used in relatively healthy people or in surgical patients compared with septic patients. Surgical patients tend to have less capillary leakage than septic patients, who show considerable amounts of HES distributed in the interstitial space, which likely contributed to the observed increase in late nephrotoxicity or mortality [15]. In fact, the reported administered volume ratio (crystalloids to colloids ratio) was decreased to only 1.1 to 1.4 over the first 4 days in patients with severe sepsis [1]. Furthermore, it is not known which doses are safe, even though there has been no evidence of renal impairment with lower HES doses [16]. Historically, dose limits for HES were set in accordance with the dose limits for dextran, because it was found that both colloids affected coagulation to a similar degree [8].

Hüter et al. [17] found that hexastarch had a greater pro-inflammatory effect than tetrastarch and caused more pronounced tubular damage than the latter in an isolated porcine renal perfusion model. Renal interstitial proliferation, macrophage infiltration, and tubular damage were identified as potential pathological mechanisms of HES-induced nephrotoxicity. Neuhaus et al. [18] reported a concentration-dependent decrease in the viability of the human renal proximal tubular cell (PTC) line HK-2 after incubation with tetrastarch for 21 h. In particular, 0.5 % and 4 % tetrastarch decreased cell viability to an average of 86.8 % and 24.02 %, respectively. In contrast, Silva et al. [19] recently reported that a tetrastarch [HES 130/0.42 in Ringer's acetate (RAc)] after major hemorrhage yielded no major effect on plasma neutrophil gelatinase-associated lipocalin (NGAL) levels and histopathological acute kidney injury (AKI) scoring compared with RAc alone in a pig experimental model of acute lung injury. Additionally, there was a conflicting experimental report in ovine endotoxin shock showing that renal function, as assessed by creatinine clearance and cumulative creatinine excretion as well as ultrastructural tubular integrity, is preserved with the use of balanced HES130/0.42 (up to a maximum dose of 50 ml/kg) despite increases in plasma creatinine and urea concentrations [20]. Accordingly, extrapolating these in vitro findings to the clinical setting is of limited value, because tetrastarch is degraded and eliminated in the clinical setting in a different manner from that determined in in vitro experiments. It is also unclear whether the changes detected in in vitro experiments are irreversible and thus responsible for AKI.

Nephrotoxicity in septic patients

Two large prospective trials published in 2012, the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial and the Crystalloid versus Hydroxyethyl Starch Trial (CHEST), had a huge impact on the use of tetrastarch in intensive care [21, 22]. The 6S trial was conducted with 804 patients at 26 hospitals and evaluated the effect of a tetrastarch (HES 130/0.42) in RAc compared with RAc alone at a dose of up to 33 ml/kg/day of ideal body weight [21]. In patients with severe sepsis, those in the tetrastarch group had an increased risk of death at 90 days after fluid resuscitation (RR = 1.17; $p = 0.03$) and were more likely to require renal replacement therapy (RR = 1.35; $p = 0.04$) and blood transfusion (RR = 1.52; $p = 0.09$) than those in those RAc group. CHEST was conducted with 7,000 patients at 32 hospitals in Australia and New Zealand and evaluated the effect of a tetrastarch (HES

130/0.4) in normal saline compared with normal saline alone on mortality after 90 days, even though the study protocol allowed for fluid infusion until day 90 after randomization [22]. Less fluid on the first study day was administered in the tetrastarch group (about 1.0 l) than in the normal saline group (1.2 l). In contrast to the 6S trial, no significant differences in mortality were seen between the study fluids [relative risk (RR) = 1.06; $p = 0.26$]. However, more patients in the tetrastarch group (7.0 %) required renal replacement therapy than in the normal saline group (5.8 %) (RR = 1.21; $p = 0.04$) despite having a lower rate of AKI as judged by the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria [23]. On the basis of the data obtained in these two trials, the Surviving Sepsis Campaign guidelines of 2012 and review articles recommend against the use of HES solutions in the resuscitation of patients with severe sepsis or septic shock [2–6, 24].

Kidney function in surgical patients

Studies including meta-analyses focusing exclusively on renal function after the intraoperative use of a tetrastarch published between January 2012 and August 2013 were searched for via PubMed. The criteria for the eligible studies were the intraoperative use of tetrastarch and kidney function. Seven studies consisting of two reviews and five single trials met the criteria (Table 2).

Van Der Linden et al. [15] analyzed 38 publications related to renal function after the intraoperative administration of a tetrastarch. Among them, 21 reported on serum creatinine concentrations or creatinine clearance after the administration of test fluids. In studies involving high-risk surgeries and kidney transplantation, 1,005 patients were given a tetrastarch and 1,051 patients were given a comparator. Unfortunately, carrier solutions for tetrastarch were not indicated in detail, and comparators included not only albumin and crystalloids, but also other synthetic colloids and older starches. The period for which creatinine was reported varied by up to 14 days after administration. Overall, no differences in the tested markers were noted between a tetrastarch and any of the other tested fluids. The ratio of peak serum creatinine in the tetrastarch group to that in the other groups varied from 0.86 to 1.08. Regarding high-risk surgical procedures such as kidney or liver transplantation and abdominal aortic surgery, no significant differences were observed in serum creatinine or creatinine clearance between the two groups. Additionally, the requirement for renal replacement therapy in 7 studies did not differ between the groups: 7 of 388 (1.8 %) patients received a tetrastarch and 12 of 402 (3.0 %) received a comparator ($p = 0.35$).

Martin et al. [25] reported a meta-analysis of 17 randomized studies involving 1,230 patients undergoing a variety of elective surgical procedures. A tetrastarch was compared with a comparator. Although carrier solutions for tetrastarch were not indicated in detail, comparators included normal saline, Ringer's solution, and albumin as well as older starches and other synthetic colloids. Although only 3 of the included studies (2 on cardiopulmonary bypass and 1 on liver transplantation) showed a slight increase in serum creatinine that occurred on average 2 days after surgery, no significant differences were noted between the tetrastarch and respective comparators with regard to calculated creatinine clearance, incidence of acute renal failure, or mortality, despite a high heterogeneity of creatinine values ($I^2 = 68.5$ % for baseline values vs. $I^2 = 79.8$ % for extreme values). The authors, however, recognized that their findings could not be extrapolated to the use of tetrastarch when fluid resuscitation of donors or recipients is required during kidney transplantation.

Feldheiser et al. [26] compared a tetrastarch in balanced electrolyte solution with a balanced electrolyte solution alone during cytoreductive surgery for ovarian cancer. Each fluid was given up to the dose limit (50 ml/kg) to optimize stroke volume according to a goal-directed hemodynamic algorithm. The tetrastarch group showed better hemodynamic stability and reduced need for fresh frozen plasma. Perioperative plasma creatinine levels and NGAL as renal injury markers were similar in both groups, even though intraoperatively administered fresh frozen plasma may have also affected postoperative renal function.

Gurbutz et al. [27] prospectively compared a tetrastarch in normal saline with a balanced electrolyte solution alone used as a prime solution for cardiopulmonary bypass in coronary artery bypass surgery (1,500 ml). Although postoperative renal dysfunction was defined as a peak creatinine value of $\geq$1.5 times the preoperative value, the incidence of renal dysfunction did not differ between the groups ($p = 0.421$).

Van Der Linden et al. [28] compared a tetrastarch in normal saline and 5 % human albumin alone during elective pediatric cardiac surgery and demonstrated that the incidence of adverse events up to postoperative day 28 did not differ between the groups. They also showed that new renal biomarkers increased in both groups without significant differences, even though the postoperative sampling dates varied between patients.

Akkucuk et al. [29] conducted a prospective study in pediatric cardiac surgical patients. Either a tetrastarch in normal saline or lactated Ringer's solution was administered as a prime solution for cardiopulmonary bypass. No renal dysfunction as defined by Gurbutz et al. [27] was observed in either group. Additionally, there was no

Table 2 Recent publications on postoperative kidney function following the intraoperative use of 6 % tetrastarches compared with other solutions

Study, year	Raw material	No. of trials (patient numbers)	Clinical setting	Marker or criteria	Results	Study period
Van der Linden [15], 2013 meta-analysis	Waxy maize or potato	7 (863)	Major vascular surgery, trauma, coronary artery bypass, liver transplantation, hip arthroplasty	Need RRT	Odds ratio 0.60, 95 % CI (0.23–1.53), $p = 0.35$	Varied up to 14 days
		21 (2,098)	Major surgery including cardiac, liver, major spine, vascular, surgeries, CPB and kidney transplantation	Peak sCr ratio in the tetrastarch group to the comparator group	Odds ratio 1.0, 95 % CI (1.0–1.0)	
Martin [25], 2013 meta-analysis	Waxy maize	17 (1,230)	Elective surgery, including CPB, cardiac surgery, liver transplantation	Maximum sCr	Effect size 0.068, 95 % CI (−0.227 to 0.362), $p = 0.65$	On average 2 days
				Calculated CCr		
				ARF (RIFLE criteria)	Pooled risk difference 0.302, 95 % CI (−0.098 to 0.703), $p = 0.14$	
				Need RRT		
					Pooled risk difference 0.0003, 95 % CI (−0.018 to 0.019), $p = 0.98$	
					Pooled risk difference 0.003, 95 % CI (−0.028 to 0.022), $p = 0.98$	
Feldheiser [26], 2013 randomized study	Waxy maize	1 (50)	Cytoreductive surgery for ovarian cancer	sCr	No difference, $p = 0.4289$	4 months
				Plasma NGAL	No difference, $p = 0.7629$	3 months
Gurbutz [27], 2013 randomized study	Waxy maize	1 (200)	CPB priming for coronary artery bypass	Max sCr ≥ 1.5 times than basal value	No difference, $p = 0.421$	Not described
Akkucuk [29], 2013 randomized study	Waxy maize	1 (24)	Elective pediatric cardiac surgery (2–16 years), CPB priming	β2-MG, cystatin C, sCr, BUN, urine albumin, urinary albumin/uCr and FENa	No difference in each tested marker, *p*: not described	2 days
Van Der Linden [28], 2013 randomized study	Waxy maize	1 (60)	Elective pediatric cardiac surgery (2–12 years), including CPB priming	α-1-microglobulin/uCr	No difference, $p = 0.2257$	Not described
				β-NAG/uCr	No difference, $p = 0.9234$	
				NGAL/uCr	No difference, $p = 0.143$	
				Urinary albumin/uCr	No difference, $p = 0.1313$	
Ishikawa [30], 2012 retrospective study	Waxy maize, tetrastarch or pentastarch	1 (1,129)	Lung resection	AKI (AKIN criteria)	Odds ratio 1.5, 95 % CI (1.1–2.1). $p = 0.01$	3 days

RRT renal replacement therapy, *CI* confidence interval, *sCr* serum creatinine, *CPB* cardiopulmonary bypass, *CCr* creatinine clearance, *ARF* acute renal failure, *RIFLE* risk, injury, failure, loss and end-stage, *NGAL* neutrophil gelatinase-associated lipocalin, *β2-MG* β2-microglobulin, *BUN* blood urea nitrogen, *FENa* fractional excretion of Na, *β-NAG N*-acetyl-β-D-glucosaminidase, *uCr* urinary creatinine, *AKI* acute kidney injury, *AKIN* acute kidney injury network

difference in renal injury markers between the groups up until 48 h postoperatively.

In contrast to the foregoing studies, Ishikawa et al. [30] reported HES-induced nephrotoxicity. They retrospectively assessed the incidence and risk factors of postoperative AKI defined by the Acute Kidney Injury Network (AKIN) criteria [31] within the first 72 h after lung resection surgery. Exposure to HES (tetrastarch or pentastarch) in normal saline exhibited a dose-dependent effect on the occurrence of AKI with each 250-ml aliquot, increasing the odds of AKI by 1.5 fold ($p = 0.01$), although the authors did not distinguish between the different types of HES products used.

Additionally, Bayer et al. [32] have recently reported a prospective sequential study on resuscitation fluids in 6,478 cardiac surgical patients. Each tested fluid was administered sequentially for approximately 2 years [tetrastarch (HES 130/0.4) from 2004 to 2006, 4 % gelatin from 2006 to 2008, and crystalloids from 2008 to 2010] as a fluid bolus to achieve preset hemodynamic goals not only intraoperatively, but also postoperatively in the intensive care unit, and thus this study did not meet the criteria for the eligible studies. However, renal failure defined by RIFLE criteria [23] "failure" occurred more often in the tetrastarch period than in the crystalloid period (9.2 % vs. 5.7 %, $p < 0.001$). Risk of renal replacement therapy was greater after tetrastarch compared to crystalloid (OR = 2.29; $p < 0.001$). Using the Simplified Renal Index Score, which is used to predict renal replacement therapy after cardiac surgery [33], patients in the tetrastarch period who met the criteria of the high-risk (4 points) category had greater use of renal replacement therapy compared to patients in the crystalloid period ($p < 0.001$).

In summary, most of the recent studies did not show nephrotoxicity following the intraoperative use of a tetrastarch, even though it was demonstrated in one retrospective study and one sequential perioperative study.

Carrier solutions

Normal saline solution is commonly used as a tetrastarch carrier solution. High infusion volumes of normal saline, however, may lead to hyperchloremia and metabolic acidosis [34, 35]. Additionally, hyperchloremia itself has a renal vasoconstrictive effect that reduces glomerular filtration rate [36]. In contrast, administering a balanced electrolyte solution has been reported to improve the viability of human renal PTC line HK-2 in vitro compared with normal saline [18]. Furthermore, even healthy volunteers can take up to 2 days to excrete a rapid infusion of 2 l normal saline [37]. In critically ill patients, the capacity to excrete a salt and water load is further impaired [38]. Yunos et al. [39] recently showed that the implementation of a chloride-restrictive strategy in critically ill adults was associated with a significant decrease in the incidence of AKI and the use of renal replacement therapy. Therefore, balanced electrolyte solutions, but not normal saline, are recommended as a tetrastarch carrier solution.

Criticism against the two large trials in septic patients

There are several limitations of the 6S trial and CHEST [21, 22]. First, in contrast to CHEST, a considerable number of eligible patients of either group (35–36 %) in the 6S trial were associated with AKI before enrollment, even though renal failure with oliguria or anuria not related to hypovolemia is a contraindication of tetrastarch (prescribing information for HES).

Second, fluid volume resuscitation in the 6S trial was decided at the discretion of the intensive care unit physician. In contrast, the judgment of fluid volume resuscitation in CHEST was based on cardiac filling pressures, which have been clearly shown to be unreliable markers of cardiac preload or fluid responsiveness in critically ill patients [40]. Accordingly, some patients in these studies may have received fluid overload. As tetrastarches rather than crystalloids have a greater effect on plasma volume expansion, Ertmer et al. [41] speculated that hemodilutional effects without evidence of hemorrhage would lead to increased blood transfusion following the use of tetrastarch. The tetrastarch group in the 6S trial received as much as 1 l tetrastarch, even on day 3, suggesting the possible presence of fluid overload rather than goal-directed fluid therapy. As fluid overload itself may have harmful effects on late kidney function [42], fluid volume should be administered based on more reliable markers.

Third, the endpoint of fluid volume administration was not clearly defined in these two trials. In the 6S trial, most patients were resuscitated before enrollment as suggested by a median central venous pressure of 10 mmHg, a relatively low plasma lactate level, and a prerandomization infusion volume >3 l. In comparison, CHEST enrolled patients an average of 11 h after admission to the intensive care unit.

Fourth, the decision for renal replacement therapy in both trials was not predefined and was therefore subjective. In CHEST, more frequent dialysis in the tetrastarch group despite a higher rate of AKI based on the RIFLE criteria [23] in the normal saline group allows us to speculate that the initiation of dialysis is a weak study endpoint.

Finally, Phillips et al. [43] raised additional concerns about CHEST findings. Disease severity was lower than in the 6S trial, and elective surgical patients were included in CHEST. In addition, the time to resolution of the objective

parameters used to support a diagnosis of hypovolemia was not compared between the groups. Unfortunately, neither of these trials took into account the potential benefit of colloids in patients with severe hypovolemia requiring rapid correction with low fluid volume, even though they addressed late adverse outcome [38, 43].

An article by Ertmer et al. [41] discusses two recently completed studies on renal function in intensive care patients and severe sepsis patients. Colloids Compared to Crystalloids in Fluid Resuscitation of Critically Ill Patients ($n = 2{,}857$) and the Basel Starch Evaluation Study ($n =$ approximately 240) addressed, at least partly, the limitations in the 6S trial and CHEST. As neither of these new studies has yet been published, it would seem prudent on the basis of current evidence to avoid the use of tetrastarches in patients with severe sepsis or septic shock.

Criticism against studies in the surgical setting

There are several limitations of recent surgical studies on HES-related nephrotoxicity. First, the authors of the recent surgical trials acknowledge their small sample sizes [15, 25, 30], and Martin et al. [25] recognizes sample size and power of the study as limitations of any meta-analysis. With the exception of one retrospective observational study of 1,129 patients [30], studies in the surgical setting have had smaller sample sizes than the trials conducted in the intensive care setting. Presumably, such small sample sizes would typically exaggerate outcomes in either direction [6]. According to exemplary sample size calculations for safety endpoints of AKI in cardiac surgical patients, each study requires 1,000 patients divided into two arms [8].

Second, the study periods were too short for most of the studies involving surgical patients. Accordingly, most of these studies might have ended before any suspicion was raised of possible long-term adverse effects. In fact, in the 6S trial, no difference in survival was observed until 60 days after HES administration but a significant difference was found on further follow-up to 90 days [21]. The longest follow-up period was reported in recent surgical studies was 4 months after the use of a tetrastarch [26]; the remaining studies were completed up to the first few postoperative days or did not describe sampling dates. Therefore, a longer follow-up period of at least 3 months is needed to detect the late adverse renal dysfunctions.

Third, most studies used serum creatinine levels or their change as a renal injury marker. The RIFLE criteria [23] or AKIN criteria [31], which can diagnose AKI more reliably than serum creatinine-based criteria, were used in only a few studies involving surgical patients. These criteria, however, have known limitations, as serum creatinine levels are neither sensitive nor specific and tend to represent functional changes rather than be a true marker of kidney injury [9]. In this context, new biomarkers such as NGAL would be of clinically relevant value as better markers for detecting AKI before serum creatinine levels are elevated. To date, only three studies have used these new biomarkers [26–28].

Fourth, there have been few studies on high-risk surgical patients, even though some studies have included elective cardiac, hepatic, renal, or major vascular surgical patients. Additionally, tetrastarch doses in the surgical setting may be lower for critically ill patients. Finally, there is a concern about the raw materials of tetrastarches [44]. Potato-derived starch in contrast to waxy maize-derived starch contains several thousand parts per million of esterified phosphate groups. By adding further negative charges to the original starch molecules, the longer starch chain may affect the tertiary structure and contribute to the higher viscosity of potato-derived starch. It is still unclear, however, whether these marked biochemical differences between the two different raw materials have different clinically relevant outcomes.

Conclusions

Six of seven recent studies did not show nephrotoxicity following the intraoperative use of tetrastarch. However, data are not sufficiently robust to conclude that tetrastarches are safe for renal function. Large prospective randomized trials with longer follow-up periods are required to resolve the clinically relevant concerns. Moreover, balanced electrolyte solutions are strongly recommended as a carrier solution for tetrastarch to reduce the adverse outcomes.

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