

**The Use of Two Modern Hydroxyethyl
Starch Solutions in Major Urological
Procedures: Effect on Acid-Base Status
and Renal Functions**

Submitted for fulfillment of the degree of MD in Anesthesiology

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Abstract

This study showed that both balanced 6% HES 130/0.4 (Tetraspan) and saline-based 6% HES 130/0.4 were equally effective for hemodynamic stabilization of patients undergoing major urologic procedures without any significant impact on acid base or renal functions. In the context of safety concerns that has been raised recently regarding the use of HES in critically ill patients, it is time to reevaluate the safety of using HES intraoperatively and whether we still need to continue using these solutions or not. The third generation of tetrastarches shows a significantly improved safety profile without any loss of volume effect compared to first- and second-generation HES preparations.

Keywords

ARF, CMDh, AKIN, Hydroxyethyl, ADQI, AKI,

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List of Abbreviations

ADQI	Acute Dialysis Quality Initiative
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ALT	Alanine transaminase
ARF	Acute renal failure
ASA	American Society of Anesthesiologists
AST	Aspartate transaminase
AUC	Area under the plasma concentration curve
BEST	Beginning and Ending Supportive Therapy
BUN	Blood urea nitrogen
C	Carbon atom
CKD	Chronic kidney disease
C_{max}	Maximum plasma concentration
CMDh	The Coordination Group for Mutual Recognition and Decentralised Procedures – Human
CPB	Cardiopulmonary bypass
CrCl	Creatinine clearance
CVP	Central venous pressure
d	Day

dl	Deciliter
DM	diabetes mellitus
DS	Degree of substitution
ELAM	Endothelial leukocyte adhesion molecule
ESRD	End Stage Renal Disease
FFP	Fresh frozen plasma
FiO₂	Fraction of inspired oxygen
g	Gram
GFR	Glomerular Filtration Rate
G_s	Number of substituted anhydroglucose residues
G_t	Total number of anhydroglucose residues in the polymer
h	Hour
HCO₃	Bicarbonate
HES	Hydroxyethyl starches
ICAM	Intercellular adhesion molecule
ICU	Intensive care unit
IHD	Ischemic heart disease
IL	Interleukin
INR	International Normalized Ratio
kDa	KiloDalton

kg	Kilogram
l	liter
m²	Square meter
MAP	Mean arterial blood pressure
MDRD	Modification of Diet in Renal Disease
mg	Milligram
min	Minute
ml	Milliliter
mmHg	Millimeter of mercury
mmol	Millimole
Mn	Number averaged MW
MS	Molar substitution
MW	Molecular weight
Mw	Weight averaged MW
na	Value not stated in source publication
NaCl	Sodium Chloride
ng	Nanogram
NGAL	Neutrophil Gelatinase-Associated Lipocalin
PCO₂	Partial Pressure of Carbon Dioxide
pg	Picogram
PICARD	Program to Improve Care in Acute Renal Disease

PO₂	Partial Pressure of Oxygen
ppm	parts per million
PRAC	Pharmacovigilance Risk Assessment Committee
PRAC	Pharmacovigilance Risk Assessment Committee
RRT	Renal Replacement Therapy
SAPS	Simplified Acute Physiology Score
SCC	Squamous cell carcinoma
sCr	Serum creatinine
SD	standard deviation
sELAM	Soluble Endothelial leukocyte Adhesion Molecule
sICAM	Soluble intercellular adhesion molecule
SPO₂	Oxygen saturation
T_{½central}	Elimination half-life from the central compartment
T_{½α}	Initial/distribution half-life
T_{½β}	Terminal/elimination half-life
TCC	Transitional cell carcinoma
ug	Microgram
WISEP	Efficacy of Volume substitution and Insulin therapy in Severe Sepsis study

vs

Versus

W_H

**Weight fraction of hydroxyethyl
groups in the polymer**

yr

year

α

Alpha

μmol

Micromole

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Hydroxyethyl Starches

With the development of a new generation of hydroxyethyl starches (HES), there has been renewed interest in their clinical potential. High doses of first- and second-generation HES were associated with adverse effects on renal function, coagulation and tissue storage, thereby limiting their clinical applicability. Newer HES products have lower molar substitution and in vivo molecular weight, resulting in more rapid metabolism and clearance.

A recent systematic review of randomized clinical studies on the use of fluid therapy in various types of surgical procedures found no evidence to recommend one type of fluid therapy over another. Neither was there sufficient evidence to provide guidance on the optimal amount of fluid to use in elective surgical procedures.¹ It was therefore concluded that guidelines for perioperative fluid management must be procedure specific; in the absence of firm evidence for one approach or another, individualized, goal-directed fluid administration should be used.²

Despite the absence of clear recommendations for any particular fluid therapy, there is plentiful debate about the relative merits of crystalloid or colloid, and even about different types of colloids.³

Development of HES: Hetastarch to Tetrastarch

The first HES product, i.e., Hespan® (DuPont Pharmaceuticals, Wilmington, DE), was made available in the United States in the 1970s. Since then, further generations of HES have been developed, differing in their mean molecular weight (MW), molar substitution (MS), and C2/C6 ratio. Hydroxyethyl starches are identified by three numbers, e.g., 10% HES 200/0.5 or 6% HES 130/0.4.⁴

The first number indicates the concentration of the solution, the second represents the mean MW expressed in kiloDalton (kDa), and the third and most significant one is MS. These parameters are highly relevant to the pharmacokinetics of HES (table 1).⁴

Concentration

Concentration mainly influences the initial volume effect: 6% HES solutions are iso-oncotic in vivo, with 1:1 replacing about 1:1 of blood loss, whereas 10% solutions are hyperoncotic, with a volume effect considerably exceeding the infused volume (about 145%).⁴

Molecular Weight

In common with all of the synthetic colloids, HES are polydisperse systems containing particles with a wide range of molecular mass. In polydisperse systems, the determination of particle mass or relative molecular mass gives averages, which depend on the method used. The MW can be described in one of two ways: weight averaged MW (M_w) and number averaged MW (M_n).⁴

Table 1: Characteristics of Hydroxyethyl Starch (HES) Preparations

	Concentration and Solvent	Mean Molecular Weight, kDa	Molar Substitution	C ₂ /C ₆ Ratio	Maximum Daily Dose, ml/kg
HES670/0.75	6% balanced solution	670	0.75	4.5:1	20