ABBOTT

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May 24, 2002

Food and Drug Administration
Center for Biologics Evaluation and Research
Division of Blood Products, HFM-302
Woodmont Office Center, Suite 400 North
1401 Rockville Pike
Rockville, MD 20852

Attention: Dr. Linda Smallwood
VIA E-Mail: smallwood@cber.fda.gov
VIA Fax: (301) 827-2843

Re: Hextend ® (6% hetastarch in lactated electrolyte injection, Abbott; HTX) NDA 20-0952
Blood Products Advisory Committee Meeting June 13 and 14, 2002
Hetastarch Safety Publications and Draft Publications for Consideration

Dear Dr. Smallwood:
Abbott Laboratories would like to request that the attached confidential executive summary with the accompanying bibliography confidential article copies be submitted to the Blood Products Advisory Committee for consideration prior to the June 14th meeting. All information is to be considered to be confidential to the Blood Products Advisory Committee only! Abbott also requests 30 minutes for public comments and presentations during the 12:00-12:30 time on June 14th. Our comments will be to address the existing safety information and pre-publication information regarding the evidence for excessive bleeding during cardiac surgery in patients treated with hetastarch compounds, and to make recommendations for the unwarranted need for warning statements for risk of excessive bleeding during cardiac surgery in the Hextend® package insert. Abbott's 3 speakers to be confirmed by the June 3rd notification date will include noted practitioners in the field of cardio-thoracic surgery, with extensive experience using hetastarch compounds.

Abbott has prepared an executive summary for the advisory committee and has attached copies of the publications within the executive summary including:

1. Hextend® Package Insert
2. Bennett-Gurerrero E., Frumento R. J., Mets B, et al. Impact of normal saline based versus balanced salt intravenous fluid replacement on clinical outcomes: A randomized blinded clinical trial. *Anesthesiology* 2001; 95; Abstract 147
3. Issues in Fluid Volume Replacement. *Anesthesiology News* 2002: 28: 1-8
4. Petroni K. C., Green R., and Birmingham S. Hextend® is a safe alternative to 5% human albumin for patients undergoing elective cardiac surgery. *Anesthesiology* 2001; 95; Abstract 198
5. Martin G., Bennett-Guerrero E., Wakeling H., et al. A prospective randomized comparison of thromboelastographic profile in patients receiving lactated Ringer's solution, 6% hetastarch in saline during major surgery. *JcardThorAn* (in press-**confidential**)
6. Roche A. M., Mythen M. G., and James M. F. M., Grocott M. P. W., et al. Coagulation effects of *in vivo* serial haemodilution with a balanced electrolyte hetastarch solution

compared with a saline-based hetastarch solution and lactated Ringer's solution. *Anaesthesia* (in press-confidential)

7. Roche A. M., Mythen M. G., and James M. F. M.. Comparison of the coagulation effects of balanced electrolyte versus saline-based haemodilution using TEG *in vitro*. *Anesthesiology* 2001; 95; Abstract 199
8. Treib J., Baron J. F., Grauer M. T., et al. An international view of hydroxyethyl starches. *Intensive Care Med* 1999; 25: 258-268.

I trust you will find the enclosed information satisfactory for pre-read presentations to the advisory committee. Should you have any questions regarding this correspondence please contact me at the address above, by telephone at (847) 938-8983, or by fax at (847) 938-7867.

Thanks for your time and consideration.

Sincerely,
ABBOTT LABORATORIES

James R. Wangelin
Regulatory Affairs Associate Director
Hospital Products Division
D-0389, J45-2

JRW:me

Enclosures

Abbott Executive Summary

Executive Summary References:

#1: Hextend® Package Insert

#2: Impact of normal saline based versus balanced salt intravenous fluid replacement on clinical outcomes: A randomized blinded clinical trial abstract

#3: Issues in fluid volume replacement article

#4: Hextend® is a safe alternative to 5% human albumin for patients undergoing elective cardiac surgery abstract

#5 A prospective randomized comparison thromboelastographic profile in patients receiving lactated Ringer's solution, 6% hetastarch in saline during major surgery draft article

#6 Coagulation effects of *in vivo* serial haemodilution with a balanced electrolyte hetastarch solution draft article

#7 Comparison of the coagulation effects of balanced electrolyte versus saline-based haemodilution using TEG *in vitro* abstract

#8 An international view of hydroxylethyl starches article

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Abbott Laboratories Executive Summary
(7 pages)

Executive Summary Abbott Laboratories
Blood Products Advisory Committee June 13-14, 2002

Introduction

The Food and Drug Administration (FDA) has asked if evidence for excessive bleeding in cardiac surgery patients is strong enough to warrant a warning statement in the hetastarch labeling.

The information submitted includes data supplemental to materials sent to the Agency in response to a letter dated July 23, 2001 from Dr. Mark Weinstein of the Office of Blood Research and Review. Citing retrospective studies, the letter inquired about a possible association with the use of 6% hetastarch in cardiac surgery and excessive bleeding.

This paper describes a recently completed, prospective randomized controlled trial of volume expanders in cardiac surgery that documented coagulation outcomes. The study is in the submission process for publication. Additional research, both in surgical patients and *in vitro,* supports the conclusions of the cardiac study.

Data regarding clinically relevant bleeding and coagulation kinetics is given greater weight than changes in laboratory values. Based on the results of these studies, a warning label on Hextend for excessive bleeding in cardiac surgery is not appropriate.

Background

Currently, there are two approved formulations of 6% hetastarch in the United States. The electrolyte compositions are as follows:

Electrolyte (mEq/L)	Hextend	HNS
Sodium	143	154
Chloride	124	154
Lactate	28	0
Calcium	5	0
Potassium	3	0
Magnesium	0.9	0
Dextrose (mg/L)	990	0

Hextend® (6% hetastarch in lactated electrolyte injection, Abbott; HXT) was approved for marketing on March 31, 1999 (NDA 20-0952). It is indicated for the treatment of hypovolemia when plasma volume expansion is desired. The plasma volume expansion produced by Hextend approximates that produced by 6% hetastarch in 0.9% sodium chloride injection (HNS) which in turn approximates that of 5% albumin (Human)[1]. The electrolyte composition resembles the principal ionic constituents of normal plasma.

Published studies that have hypothesized an association of excessive bleeding in cardiac surgery with hetastarch have only evaluated the HNS product. These studies have primarily been retrospective analyses or studies with small sample sizes. Retrospective analyses have limitations as clinical practices change over time or may be variable among practitioners. They are not randomized and blinded trials, therefore statistical validity is questionable for hypothesis testing. The papers call for prospective, randomized controlled clinical studies, which would be statistically valid to determine the impact of hetastarch on bleeding in cardiovascular surgery.

A randomized, double blind, prospective study in cardiac surgery patients was recently completed and is in the publication process. Data in the public domain is presented below.

Cardiac Surgery

Dr. Elliott Bennett-Guerrero of Columbia University completed a randomized, double-blind, controlled trial in 200 patients undergoing cardiac bypass graft and/or valvular heart surgery that compared four fluids used for intraoperative volume replacement[2,3]. The four groups were (1) 5% albumin in a sodium chloride based vehicle-ALB (2) 6% hetastarch in 0.9% sodium chloride-HNS (3) Hextend-HXT and (4) lactated Ringer's-LR. Patients received the study fluid throughout the procedure including the prime. Mean volume of study fluid administered was 3.5L.

Results indicated that patients receiving HNS experienced greater coagulopathy compared to the other groups. HXT and ALB patients had similar outcomes with respect to coagulation.

	LR	ALB	HXT	HNS
PRBC transfused (OR+24h)*	1(0-4)	2(0-4)	2(0-4)	4(2-6)
Units FFP transfused (OR+24h)*	0(0-0)	0 (0-0)	0(0-4.5)	3(0-6)
Units Platelets transfused(OR+24h)*	0(0-6)	0(0-6)	0(0-6)	6(0-9)
% Receiving platelets or FFP (OR+24h)*	26	42	47	69
Return to OR for coagulopathy	0	2%	2%	8%

*$p<0.0001$

Median (interquartile range) are shown except where indicated

Sodium chloride based fluids (ALB, HNS) exhibited inferior renal function indices (serum creatinine, creatinine clearance, urine output) when compared to LR and HXT ($p<0.0001$).

At the Naval Hospital in San Diego, Petroni and colleagues studied 28 cardiopulmonary bypass patients who were randomized to either Hextend or albumin diluted to a 5% concentration with lactated Ringer's[4]. The study period was from the time the patient was taken off bypass to 24 hours postoperatively. The objective was to determine if there was any difference in coagulation parameters between the two plasma volume expanders.

Blood samples for thromboelastography (TEG) were drawn before induction, end of surgery (post protamine), and on postoperative day #1. In addition chest tube output was measured every four hours and blood product usage recorded preoperatively, post-protamine intraoperatively, and on postoperative day #1. Patient demographics, laboratory data and hemodynamics were also documented for those time periods.

Fourteen patients were evaluated in each group. There was no statistical difference in TEG data (r time, k time, maximum amplitude, coagulation index) intraoperatively and post-op day #1. There was no statistical differences in chest tube output, pre- or post-op Hct or blood product usage. Age, sex, total CPB time, total colloid transfused were similar between groups.

Thromboelastograph Studies

Martin et al [5] compared the effects of LR, HNS, and HXT on coagulation with thromboelastography (TEG). Ninety patients (30/group) undergoing non-cardiac surgery with an anticipated blood loss of >500 mL were administered study fluid intraoperatively based on an algorithm to maintain hemodynamics. Target values were established for urine output, maintenance of arterial blood pressure, and heart rate. Blood products were given as needed.

TEG r time (rate of initial fibrin formation), k time (time for a fixed degree of viscoelasticity in the forming clot), maximum amplitude (absolute strength of the fibrin clot), and alpha angle (rate at which clot is formed) were measured at anesthesia induction, end of surgery, and 24 hours postoperatively.

Results demonstrated that HNS patients had a hypocoagulable state with prolongation of the r and k times and a reduction in maximum amplitude. This normalized by day 1 postoperatively. LR administration was associated with a hypercoagulable condition with reductions in the r and k times and increase in maximum amplitude. This continued up to postoperative day 1. HXT patients had the least change in TEG at the end of surgery with a reduction in r time at postoperative day 1.

There was no significant difference between groups in the amount of red cells, FFP, cryoprecipitate, or platelets administered; no significant difference was noted in estimated blood loss. The mean volume of study fluids administered ± SD were HNS (1301 ± 1079 mL), HXT (1448 ± 759 mL) and LR (5946 ± 1909 mL).

The paper has been accepted for publication in the *Journal of Cardiothoracic and Vascular Anesthesia*. A confidential galley proof is provided in the bibliography.

Roche et al[6] evaluated the coagulation effects of *in vitro* serial hemodilution using HXT, HNS, and LR. Five healthy volunteers donated two samples per day of fresh whole blood on two separate days using a two-syringe technique from a free-flowing vein. The fresh whole blood was immediately mixed with increasing volumes of HXT, HNS, and LR. Dilutions were 20, 30, 40, 50, 60, and 75% prepared in polypropylene tubes with a total volume of 1 mL. Undiluted fresh whole blood was used as control. Each TEG sample was allowed to run for a minimum of 60 minutes or until the maximum amplitude was reached.

HXT showed an enhanced coagulation profile (r and k times, alpha angle) at 20-40% dilution with a decrease in overall coagulation at higher dilution. LR had a biphasic response as well with significant changes in the alpha angle. HNS had significantly increased r-times compared to HXT and LR at 40, 60, and 75% dilutions. At 50% dilution r-times for HNS were significantly increased compared to HXT. K-times were significantly longer with HNS compared to LR at 60 and 75% dilution and with HXT at 75% dilution. Alpha angles were significantly lower with HNS than with HXT or LR at 30-75% dilutions and lower than HXT at 20% dilution. Maximum amplitudes were decreased in HNS compared to LR and HXT at 60 and 75% dilution as well compared to LR at 50% dilution. LR and HXT exhibited no significant differences between groups in r-times and maximum amplitude. LR had shorter k-times at 75% dilution and smaller alpha angles at 20% dilution versus HXT.

The manuscript has been accepted for publication in *Anaesthesia* and is in the revision process. A confidential draft is provided in the bibliography.

Roche et al[7] at University College London in the United Kingdom evaluated the influence of plasma volume expanders with varying electrolyte compositions on coagulation parameters. Thromboelastography (TEG) was used to assess the effect at different hemodilutions. The plasma volume expanders studied were:

- 0.9% Sodium Chloride Injection (NS)
- Lactated Ringer's Injection (LR)
- 6% Hetastarch in 0.9% Sodium Chloride Injection (HNS)
- 6% Hetastarch in Lactated Electrolyte Injection (HXT, Hextend®)
- 6% Pentastarch in 0.9% Sodium Chloride Injection (HSTER, HAES-Steril®)
- 6% Pentastarch in Lactated Electrolyte Injection (PTL, PentaLyte®)
- 6% Hydroxyethylstarch 130/0.4 in 0.9% Sodium Chloride (VVN, Voluven®)
- Human Albumin 4.5% (ALB, sodium chloride base)

HAES-Steril, Voluven, and PentaLyte are not approved for marketing in the United States.

Fresh blood was obtained via a two-syringe technique from free-flowing veins of healthy volunteers at three intervals during a single day. This was then diluted by 20, 40, 60, and 80% with the above fluids. Control was fresh, undiluted blood. Samples were placed in a TEG analyzer six minutes after venipuncture. Samples that did not clot by 60 minutes were assigned an r-time of 60 minutes. Calcium levels were measured in all samples.

Results demonstrated no differences at 20% dilution. At 40% dilution, HNS showed prolonged r-times compared to control. All fluids except PTL had prolonged r-times compared to control at 60% dilution. ALB has no clot formation at 60 and 80% dilution. At 80% dilution, no fluid with a sodium chloride base exhibited clot formation. At the 60 and 80% dilutions, the differences in r-time between the hetastarch products HNS and HXT became more pronounced. The differences were true as well for the pentastarches PTL and HSTER. VVEN, a 130 MW starch in sodium chloride showed an increased r-time compared to both HXT and PTL at 60 and 80% dilutions.

The authors concluded that the balanced electrolyte formulations have more favorable coagulation profiles than sodium chloride based plasma volume expanders at moderate to severe dilutions.

Safety

The Hextend® safety database indicates that there are no reports related to bleeding of any type since the response regarding cardiac bleeding to the Agency in 2001. The number of units sold though April 2002 is 298,058. Assuming a daily dose of 1500 mL the estimated patient exposure is 99,352 patients exposed. This would potentially overestimate the reporting rate if patients received less than 1500 mL.

There have been no reports of bleeding or coagulopathy associated with the intraoperative administration of Hextend during cardiac surgery since the product was launched March 31, 1999. There have been two reports that contained COSTART terms relating to bleeding and/or abnormal coagulation. These incidents were during urinary tract surgery and deemed not related to Hextend administration.

The overall reporting rate for bleeding without considering alternative etiologies is:

2 reports/99,352 patients=0.0000201 reports per patient which is approximately 2 reports per 100,000 patients.

Discussion

Bleeding with hetastarch use has been debated for years. Controversy exists whether the alterations in coagulation parameters result in clinical bleeding. Until the introduction of Hextend, all studies with hetastarch were conducted in a 0.9% sodium chloride base. Hextend is a more physiologic solution than the original hetastarch formulation and it contains calcium, which is integral in the coagulation cascade. Note that in the Columbia-Presbyterian cardiac surgery study, the LR group demonstrated a potential hypercoagulable state. Hextend was similar to 5% albumin in terms of blood loss and blood product usage. HNS had the poorest bleeding outcomes compared to the other three groups. In the Naval Hospital cardiac study, there were no coagulation differences between Hextend and 5% albumin in LR, although the numbers were smaller.

The *in vitro* study data from Roche and colleagues[7] documents the impact of the electrolyte composition on coagulation. Previous literature has concluded that the molecular weight of the starch is the primary determinant of coagulation abnormalities[8]. As noted above, the research was performed with starches in a sodium chloride carrier. However, in this study the pentastarch and 130MW starch in a sodium chloride base had longer r-times at 60 and 80% dilutions than Hextend, a high molecular weight hetastarch in a more physiologic carrier.

Conclusion

In cardiac surgery patients, there is less favorable coagulation profile in patients receiving hetastarch in a sodium chloride carrier. Patients receiving Hextend demonstrated similar coagulation outcomes to those patients receiving 5% albumin.

Thromboelastographic data from multiple studies further supports the advantages of a balanced electrolyte composition in maintaining optimal coagulation parameters when used in large volumes. The impact on coagulation is not significant at smaller volumes, generally <1500 mL.

Based on the above data, a warning statement on the risk of excessive bleeding in cardiac surgery in the Hextend labeling is not warranted. Supportive clinical trials are in the publication process.

References

1. Hextend® Package Insert. Abbott Laboratories, September 1999 (58-0851-R2)

2. Bennett-Guerrero E, Frumento RJ, Mets B, et al. Impact of normal saline based versus balanced salt intravenous fluid replacement on clinical outcomes: A randomized blinded clinical trial. *Anesthesiology* 2001; 95: A147

3. Issues in fluid volume replacement (suppl). *Anesthesiology News* 2002; 28:1-8.

4. Petroni KC, Green R, and Birmingham S. Hextend® is a safe alternative to 5% human albumin for patients undergoing elective cardiac surgery. *Anesthesiology* 2001; 95: A198.

5. Martin G, Bennett-Guerrero E, Wakeling H, et al. A prospective randomized comparison of thromboelastographic profile in patients receiving lactated Ringer's solution, 6% hetastarch in a balanced-saline vehicle or 6% hetastarch in saline during major surgery. *JCardThorAn* (in press-**confidential**).

6. Roche AM, James MFM, Grocott MPW, et al. Coagulation effects of *in vitro* serial haemodilution with a balanced electrolyte hetastarch solution compared with a saline-based hetastarch solution and lactated Ringer's solution. *Anaesthesia* (in press-**confidential**).

7. Roche AM, Mythen MG, and James MFM. Comparison of the coagulation effects of balanced electrolyte versus saline-based haemodilution using TEG *in vitro*. *Anesthesiology* 2001; 95: A199.

8. Treib J, Baron JF, Grauer MT, et al. An international view of hydroxyethyl starches. *Intensive Care Med* 1999; 25: 258-68.

Executive Summary Reference #1
Hextend® Package Insert
(2 pages)

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Reported adverse reactions with isotonic solutions containing 6% hetastarch include:

General

Hypersensitivity (see ***WARNINGS***).

Death, life-threatening anaphylactic/anaphylactoid reactions, cardiac arrest, ventricular fibrillation, severe hypotension, non-cardiac pulmonary edema, laryngeal edema, bronchospasm, angioedema, wheezing, restlessness, tachypnea, stridor, fever, chest pain, bradycardia, tachycardia, shortness of breath, chills, urticaria, pruritus, facial and periorbital edema, coughing, sneezing, flushing, erythema multiforme, and rash.

Cardiovascular

Circulatory overload, congestive heart failure, and pulmonary edema (see ***PRECAUTIONS***).

Hematologic

Intracranial bleeding, bleeding and/or anemia due to hemodilution (see ***WARNINGS***) and/or Factor VIII deficiency, acquired von Willebrand's-like syndrome, and coagulopathy including rare cases of disseminated intravascular coagulopathy and hemolysis. With extensive clinical use of Hetastarch Injection, rare cases of disseminated intravascular coagulopathy and hemolysis have been observed.

Metabolic

Metabolic acidosis.

Other

Vomiting, peripheral edema of the lower extremities, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, and muscle pains. Hydroxyethyl starch-associated pruritus has been reported in some patients with deposits of hydroxyethyl starch in peripheral nerves.

DOSAGE AND ADMINISTRATION

Dosage for Acute Use in Plasma Volume Expansion

HEXTEND is administered by intravenous infusion only. Total dosage and rate of infusion depend upon the amount of blood or plasma lost and the resultant hemoconcentration as well as age, weight, and clinical condition of the patient.

Adults: The amount usually administered is 500 to 1000 mL. Doses of more than 1500 mL per day for the typical 70 kg patient (approximately 20 mL per kg of body weight) are usually not required although doses of isotonic solutions containing 6% hetastarch up to 1500 mL have been used during major surgery generally without a need for blood or blood products. Volumes in excess of 1500 mL per day have been used where severe blood loss has occurred although generally only in conjunction with the administration of blood and blood products (see ***WARNINGS***).

Pediatric Patients: Adequate, well controlled clinical trials to establish the safety and effectiveness of HEXTEND in pediatric patients have not been conducted (see ***PRECAUTIONS***, **Pediatric Use**).

General Recommendations

Do not use plastic container in series connection.

If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

This solution is intended for intravenous administration using sterile equipment. It is recommended that intravenous administration apparatus be replaced at least once every 24 hours.

Use only if solution is clear and container and seals are intact.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

If administration is by pressure infusion, all air should be withdrawn or expelled from the bag through the medication port prior to infusion.

The safety and compatibility of other additives have not been established. This product contains calcium and should not be administered simultaneously with blood through the same administration set because of the likelihood of coagulation (see ***WARNINGS***).

The solution contains no bacteriostat or antimicrobial agent and is intended only for single-dose injection. When smaller doses are required, the unused portion should be discarded.

HOW SUPPLIED

HEXTEND (6% Hetastarch in Lactated Electrolyte Injection) is supplied sterile and nonpyrogenic in 500 mL and 1000 mL single-dose flexible plastic infusion containers (List No. 1555).

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C/77°F); however, brief exposure up to 40 °C does not adversely affect the product.

Caution: Federal (USA) law prohibits dispensing without prescription.

References:

1. Diehl J., et al., Clinical Comparison of Hetastarch and Albumin in Postoperative Cardiac Patients. *The Annals of Thoracic Surgery*, 1982;34(6):674-679.
2. Gold M., et al., Comparison of Hetastarch to Albumin for Perioperative Bleeding in Patients Undergoing Abdominal Aortic Aneurysm Surgery, *Annals of Surgery*, 1990;211(4):482-485.
3. Kirklin J., et al., Hydroxyethyl Starch versus Albumin for Colloid Infusion Following Cardiopulmonary Bypass in Patients Undergoing Myocardial Revascularization, *The Annals of Thoracic Surgery*, 1984;37(1):40-46.
4. Moggio R.A., et al., Hemodynamic Comparison of Albumin and Hydroxyethyl Starch in Postoperative Cardiac Surgery Patients, *Critical Care Medicine*, 1983;11(12):943-945.
5. Damon L., Intracranial Bleeding During Treatment with Hydroxyethyl Starch, *New England Journal of Medicine*, 1987; 317(15):964-965.
6. Brutocao D., et al., Comparison of Hetastarch with Albumin for Postoperative Volume Expansion in Children After Cardiopulmonary Bypass, *Journal of Cardiothoracic and Vascular Anesthesia*, 1996;10(3):348-351.

To Open

Tear overwrap down at notch and remove solution container. Check for any leakage by squeezing solution container firmly. If leaks are found, discard solution as sterility may be impaired.

Invert container and carefully inspect the solution in good light for cloudiness, haze, or particulate matter. Any container that is suspect should not be used.

58-0851-R2-Rev. September, 1999

Printed in USA

Manufactured and Distributed by: Abbott Laboratories, North Chicago, IL 60064, USA
Under license from BioTime, Inc., Berkeley, CA 94710, USA

HEXTEND®

6% Hetastarch in Lactated Electrolyte Injection

Flexible Plastic Container

DESCRIPTION

HEXTEND® (6% Hetastarch in Lactated Electrolyte Injection) is a sterile, nonpyrogenic solution for intravenous administration. The composition, pH, and osmolarity are given in Table 1 and the electrolyte composition in Table 2.

Table 1
Each 100 mL contains

Hetastarch	6 g
Sodium Chloride, USP	672 mg
Sodium Lactate Anhydrous, USP	317 mg
Dextrose Hydrous, USP	99 mg
Calcium Chloride Dihydrate, USP	37 mg
Potassium Chloride, USP	22 mg
Magnesium Chloride Hexahydrate, USP	9 mg
Water for Injection, USP	qs

pH: approximately 5.9 with negligible buffering capacity

Calculated Osmolarity: approximately 307 mOsM

Table 2
Concentration of Electrolytes (mEq/L)

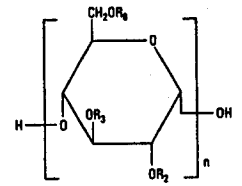
Sodium	143
Chloride	124
Lactate	28
Calcium	5
Potassium	3
Magnesium	0.9

HEXTEND (6% Hetastarch in Lactated Electrolyte Injection) is an artificial colloidal solution, pharmacologically classified as a plasma volume expander, and is intended to support oncotic pressure as well as provide electrolytes.

HEXTEND contains high molecular weight hetastarch at a concentration of 6% as an oncotic agent to permit retention of intravascular fluid until the hetastarch is replaced by blood proteins. Hetastarch is an artificial colloid derived from a waxy starch composed almost entirely of amylopectin. Hydroxyethyl ether groups are introduced into the glucose units of the starch, and the resultant material is hydrolyzed to yield a product with a molecular weight suitable for use as a plasma volume expander. Hetastarch is characterized by its molar substitution and also by its molecular weight. The molar substitution is approximately 0.75 which means hetastarch has an average of approximately 75 hydroxyethyl groups for every 100 glucose units. The weight average molecular weight is approximately 670,000 with a range of 450,000 to 800,000 and with at least 80% of the polymer units falling within the range of 20,000 to 2,500,000. Hydroxyethyl groups are attached by ether linkage primarily at C-2 of the glucose unit and to a lesser extent at C-3 and C-6. The polymer resembles glycogen, and the polymerized D-glucose units are joined primarily by α-1,4 linkages with occasional α-1,6 branching linkages. The degree of branching is approximately 1:20 which means that there is an average of approximately one α-1,6 branch for every 20 glucose monomer units.

The chemical name for hetastarch is hydroxyethyl starch.

The structural formula is as follows:



Amylopectin derivative in which R_2 and R_3 are H or CH_2CH_2OH and R_6 is H, CH_2CH_2OH, or a branching point in the starch polymer connected through an α-1,6 link to additional D-glucopyranosyl units

HEXTEND is a clear, pale yellow to amber solution. Exposure to prolonged adverse storage conditions may result in a change to a turbid deep brown or the formation of a crystalline precipitate. Do not use the solution if these conditions are evident.

HEXTEND is formulated with normal physiological levels of calcium. Calcium chloride in water dissociates to provide calcium (Ca^{++}) and chloride (Cl^-) ions. These are the normal constituents of the body fluids and are dependent on various physiologic mechanisms for maintenance of balance between intake and output. Approximately 80% of body calcium is excreted in the feces as insoluble salts; urinary excretion accounts for the remaining 20%.

HEXTEND also contains normal physiological levels of sodium. Additionally, chloride is present at levels closer to those normally found in blood than in plasma expanders in 0.9% Sodium Chloride Injection. Sodium chloride in water dissociates to provide sodium (Na^+) and chloride (Cl^-) ions. Sodium (Na^+) is the principal cation of the extracellular fluid and plays a large part in the therapy of fluid and electrolyte disturbances. Chloride (Cl^-) has an integral role in buffering action when oxygen and carbon dioxide exchange occurs in the red blood cells. The distribution and excretion of sodium (Na^+) and chloride (Cl^-) are largely under the control of the kidneys, which maintain a balance between intake and output.

HEXTEND also contains slightly lower than normal physiological levels of potassium and magnesium. Potassium chloride in water dissociates to provide potassium (K^+) and chloride (Cl^-) ions. Potassium is found in low concentrations in plasma and extracellular fluids (3.5 to 5.0 mEq/L in a healthy adult). It is the most abundant cation within the body's cells (160 mEq/L of intracellular water). Potassium plays an important role in electrolyte balance. Normally about 80 to 90% of the potassium intake is excreted in the urine with the remainder in the stools and, to a small extent, in the perspiration. The kidney does not conserve potassium well so that during fasting or in patients on a potassium-free diet, potassium loss from the body continues thereby resulting in potassium depletion.

Magnesium chloride in water dissociates to provide magnesium (Mg^{++}) and chloride (Cl^-). Magnesium is largely an intracellular ion with low concentrations (1.5 to 2.5 mEq/L) found in plasma.

Dextrose is included in the formulation. Solutions containing carbohydrate in the form of dextrose yield blood glucose, provide calories, and may also aid in minimizing liver glycogen depletion thereby exerting a protein sparing effect. Dextrose injected parenterally undergoes oxidation to carbon dioxide and water.

Lactate is provided at 28 mEq/L. Sodium lactate in water dissociates to provide sodium (Na^+) and lactate ($C_3H_5O_3^-$) ions. The lactate anion provides an alkaline effect resulting from simultaneous removal of lactate and hydrogen ions by the liver. In the liver, the lactate is metabolized to glycogen, which is ultimately converted to carbon dioxide and water by oxidative metabolism.

The lactate anion acts as a source (alternate) of bicarbonate when normal production and utilization of lactic acid is not impaired as a result of disordered lactate metabolism. Since metabolic conversion is dependent on the integrity of cellular oxidative processes, lactate may be inadequate or ineffective as a source of bicarbonate in patients suffering from acidosis associated with shock or other disorders involving reduced perfusion of body tissues. When oxidative activity is intact, one to two hours is required for metabolism of lactate.

Water is an essential constituent of all body tissues and accounts for approximately 70% of total body weight. The average normal adult daily requirement ranges from 2 to 3 L (1.0 to 1.5 L each for insensible water loss by perspiration and urine production). Water balance is maintained by various regulatory mechanisms. Water distribution depends primarily on the concentration of electrolytes in the body compartments, and sodium (Na^+) plays a major role in maintaining physiological equilibrium.

The flexible plastic container is fabricated from a specially formulated polyvinylchloride. Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. The container solution unit is a closed system and is not dependent upon entry of external air during administration. The container is overwrapped to provide protection from the physical environment and to provide an additional moisture barrier when necessary.

The closure system has two ports; the one for the administration set has a tamper evident plastic protector.

CLINICAL PHARMACOLOGY

The plasma volume expansion produced by HEXTEND approximates that produced by 6% Hetastarch in 0.9% Sodium Chloride Injection (Hetastarch Injection), and the plasma volume expansion of Hetastarch Injection in turn approximates that of 5% Albumin (Human).[1-4] In randomized, double-blind studies of Hextend versus control (Hetastarch Injection) for the treatment of hypovolemia in elective surgery, 60 patients were infused with a mean of 1596 mL of HEXTEND and 59 patients were infused with a mean of 1428 mL of Hetastarch Injection without any serious related adverse events. 59% of the HEXTEND patients and 59% of the control patients required packed red blood cells and other blood-derived products either intraoperatively or postoperatively.

Intravenous infusion of Hetastarch Injection results in expansion of plasma volume that decreases over the succeeding 24 to 36 hours. The degree of plasma volume expansion and improvement in hemodynamic state depend upon the patient's intravascular status. When administered intravenously, HEXTEND provides sources of water and electrolytes. Its electrolyte content resembles that of the principal ionic constituents of normal plasma.

Hetastarch molecules below 50,000 molecular weight are rapidly eliminated by renal excretion. A single dose of approximately 500 mL of Hetastarch Injection (approximately 30 g) results in elimination in the urine of approximately 33% of the dose within 24 hours. This is a variable process but generally results in an intravascular hetastarch concentration of less than 10% of the total dose injected by two weeks. A study of the biliary excretion of hetastarch in 10 healthy males accounted for less than 1% of the dose over a 14 day period. The hydroxyethyl group is not cleaved by the body but remains intact and attached to glucose units when excreted. Significant quantities of glucose are not produced as hydroxyethylation prevents complete metabolism of the smaller polymers.

INDICATIONS AND USAGE

HEXTEND (6% Hetastarch in Lactated Electrolyte Injection) is indicated in the treatment of hypovolemia when plasma volume expansion is desired. It is not a substitute for blood or plasma.

CONTRAINDICATIONS

Solutions containing hetastarch are contraindicated in patients with known hypersensitivity to hydroxyethyl starch or with bleeding disorders or with congestive heart failure where volume overload is a potential problem. Solutions containing hetastarch should not be used in renal disease with oliguria or anuria not related to hypovolemia.

Solutions containing lactate are NOT FOR USE IN THE TREATMENT OF LACTIC ACIDOSIS.

WARNINGS

Solutions containing calcium should not be administered simultaneously with blood through the same administration set because of the likelihood of coagulation.

Life threatening anaphylactic/anaphylactoid reactions have been rarely reported with solutions containing hetastarch; death has occurred, but a causal relationship has not been established. Patients who develop severe anaphylactic/anaphylactoid reactions may need continued supportive care until symptoms have resolved.

Hypersensitivity reactions can occur even after solutions containing hetastarch have been discontinued.

Solutions which contain potassium should be used with great care, if at all, in patients with hyperkalemia and severe renal failure and in situations in which potassium retention is present.

Solutions containing sodium ions should be used with great care, if at all, in patients with congestive heart failure and severe renal insufficiency and in clinical states in which edema with sodium retention occurs.

In patients with diminished renal function, administration of solutions containing sodium or potassium ions may result in sodium or potassium retention.

Solutions containing lactate ions should be used with great care in patients with metabolic or respiratory alkalosis. The administration of lactate ions should be performed with great care when dealing with conditions in which an increased level or an impaired utilization of these ions occurs, such as severe hepatic insufficiency.

DO NOT USE IN LEUKAPHERESIS.

Usage in Plasma Volume Expansion

Large volumes of isotonic solutions containing 6% hetastarch (HEXTEND or Hetastarch Injection) may transiently alter the coagulation mechanism due to hemodilution and a mild direct inhibitory action on Factor VIII. Hemodilution by isotonic solutions containing 6% hetastarch may also result in a 24 hour decline of total protein, albumin, and fibrinogen levels and in transient prolongation of prothrombin, activated partial thromboplastin, clotting, and bleeding times.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of isotonic solutions containing 6% hetastarch. Administration of packed red cells, platelets, and fresh frozen plasma should be considered if excessive dilution occurs.

In randomized, controlled, comparative studies of Hetastarch Injection (n = 92) and Albumin (n = 85) in surgical patients, no

patient in either treatment group had a bleeding complication and no significant difference was found in the amount of blood loss between the treatment groups.[1-4]

HEXTEND has not been adequately evaluated to establish its safety in situations other than treatment of hypovolemia in elective surgery. In some cases, the use of isotonic solutions containing 6% hetastarch has been associated with coagulation abnormalities in conjunction with an acquired, reversible von Willebrand's-like syndrome and/or Factor VIII deficiency when used over a period of days. Replacement therapy should be considered if a severe Factor VIII or von Willebrand deficiency is identified. If a coagulopathy develops, it may take several days to resolve. Certain conditions may affect the safe use of isotonic solutions containing 6% hetastarch on a chronic basis. For example, in patients with subarachnoid hemorrhage where an isotonic solution containing 6% hetastarch is used repeatedly over a period of days for the prevention of cerebral vasospasm, significant clinical bleeding may occur. Intracranial bleeding resulting in death has been reported with the use of Hetastarch Injection.[5]

PRECAUTIONS

General

The possibility of circulatory overload should be kept in mind. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated and in clinical states in which edema with sodium retention occurs.

Indirect bilirubin levels of 8.3 mg/L (normal 0.0-7.0 mg/L) have been reported in 2 out of 20 normal subjects who received multiple infusions of Hetastarch Injection. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering isotonic solutions containing 6% hetastarch to patients with a history of liver disease.

If a hypersensitivity effect occurs, administration of the drug should be discontinued and appropriate treatment and supportive measures should be undertaken (see ***WARNINGS***).

Caution should be used when administering solutions containing hetastarch to patients allergic to corn because such patients can also be allergic to hetastarch.

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, acid-base balance, and coagulation parameters during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation.

Solutions containing dextrose should be used with caution in patients with known subclinical or overt diabetes mellitus.

Caution must be exercised in the administration of parenteral fluids, especially those containing sodium ions, to patients receiving corticosteroids or corticotropin.

Potassium containing solutions should be used with caution in the presence of cardiac disease, particularly in digitalized patients or in the presence of renal disease.

Solutions containing lactate ions should be used with caution as excess administration may result in metabolic alkalosis.

Elevated serum amylase levels may be observed temporarily following administration of solutions containing hetastarch although no association with pancreatitis has been demonstrated. Serum amylase levels cannot be used to assess or to evaluate for pancreatitis for 3-5 days after administration of solutions containing hetastarch. Elevated serum amylase levels persist for longer periods of time in patients with renal impairment. Solutions containing hetastarch have not been shown to increase serum lipase.

One report suggests that in the presence of renal glomerular damage, larger molecules of hetastarch can leak into the urine and elevate the specific gravity. The elevation of specific gravity can obscure the diagnosis of renal failure.

Hetastarch is not eliminated by hemodialysis. The utility of other extracorporeal elimination techniques has not been evaluated.

If administration is by pressure infusion, all air should be withdrawn or expelled from the bag through the medication port prior to infusion.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies of animals have not been performed to evaluate the carcinogenic potential of hetastarch.

Teratogenic Effects: Pregnancy Category C.

Hetastarch Injection has been shown to have an embryocidal effect on New Zealand rabbits when given intravenously over the entire organogenesis period in a daily dose 1/2 times the maximum recommended therapeutic human dose (1500 mL) and on BD rats when given intraperitoneally, from the 16th to the 21st day of pregnancy, in a daily dose 2.3 times the maximum recommended therapeutic human dose. When Hetastarch Injection was administered to New Zealand rabbits, BD rats, and Swiss mice with intravenous daily doses of 2 times, 1/3 times, and 1 times the maximum recommended therapeutic human dose, respectively, over several days during the period of gestation, no evidence of teratogenicity was evident. There are no adequate and well controlled studies in pregnant women. HEXTEND should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether hetastarch is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HEXTEND is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of HEXTEND in pediatric patients have not been established. Adequate, well-controlled clinical trials to establish the safety and effectiveness of HEXTEND in pediatric patients have not been conducted. However, in one small double-blind study, 47 infants, children, and adolescents (ages 1 year to 15.5 years) scheduled for repair of congenital heart disease with moderate hypothermia were randomized to receive either Hetastarch Injection or Albumin as a postoperative volume expander during the first 24 hours after surgery. Thirty-eight children required colloid replacement therapy, of which 20 children received Hetastarch Injection. No differences were found in the coagulation parameters or in the amount of replacement fluids required in the children receiving 20 mL/kg or less of either colloid replacement therapy. In children who received greater than 20 mL/kg of Hetastarch Injection, an increase in prothrombin time was demonstrated ($p = 0.006$).[6] There were no neonates included in this study.

Geriatric Use

Of the total number of patients in clinical trials of HEXTEND (n=119), 30% were 65 or older while 12% were 70 or older. Other reported experience with Hetastarch Injection has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

In clinical trials comparing the plasma volume expanding properties of HEXTEND (n=60) with those of Hetastarch Injection (n=59), there were no significant differences in the number of adverse or serious adverse events between the two groups.

CONFIDENTIAL

Executive Summary Reference #2

Impact of normal saline based versus balanced salt intravenous fluid replacement on clinical outcomes: A randomized blinded clinical trial

(1 page)

A-147

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October 15, 2001
9:00:00 AM - 11:00:00 AM
Morial Convention Center, Room B

Impact of Normal Saline Based Versus Balanced-Salt Intravenous Fluid Replacement on Clinical Outcomes: A Randomized Blinded Clinical Trial

Elliott Bennett-Guerrero, M.D.; Robert J. Frumento, M.S., M.P.H.; Berend Mets, M.D., Ph.D.; Heather E. Manspeizer, M.D.; Andrew L. Hirsh, B.S.

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Background Significant controversy exists regarding the relative impact of intravenous fluids on various clinical outcomes following surgery.
Methods In a randomized blinded clinical trial, 200 cardiac surgical patients received fluid replacement intraoperatively with one of four routinely used fluids: 5% ***albumin*** in a normal saline (NS)-like vehicle, 6% hetastarch in a NS-based vehicle (Hes/NS), 6% hetastarch in a balanced-salt vehicle (Hes/BS), or lactated ringers (balanced-salt vehicle). Of note, Hes/NS and Hes/BS differ only in the composition of their vehicles.
Results Total volumes of fluid administered ($p=0.79$), cardiac output ($p=0.37$), blood pressure ($p=0.58$), and preoperative serum creatinine ($p=0.54$) were similar between groups. All indices of renal function measured (serum creatinine, urine output, creatinine clearance) were inferior in NS-based vehicle groups. Serum creatinine levels one-week postoperatively were (mg/dL, mean±SD): lactated ringers 1.0±0.4, Hes/BS 0.9±0.2, Hes/NS 1.5±0.7, ***Albumin*** 1.6±0.9 ($p<0.0001$). All 6 patients requiring hemodialysis postoperatively had been randomized to a NS-based fluid: ***albumin*** (n=2), Hes/NS (n=4). Patients administered starch-based fluids (Hes/BS or Hes/NS) exhibited less edema ($p<0.0001$), lower visual analogue pain scores ($p<0.0001$), a lower incidence of antiemetic use ($p<0.0001$), and faster return of bowel function ($p<0.0001$). The proportion of patients receiving platelets or fresh frozen plasma was significantly different ($p<0.0001$) between groups: Hes/NS (69%), Hes/BS (47%), ***Albumin*** (42%), lactated ringers (26%). Patients receiving lactated ringers crytalloid were more likely to exhibit thromboelastographic evidence (MA>68) of a hypercoagulable state and had an 8% incidence of deep venous thrombosis postoperatively. The impact of fluid type on outcome variables existed independent of whether cardiopulmonary bypass had been used.

Anesthesiology 2001; 95:A147

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Executive Summary Reference #3
Issues in fluid volume replacement
(8 pages)

This educational activity is supported through an unrestricted educational grant from

Abbott Laboratories

Based on a symposium held during the 2001 Postgraduate Assembly of the New York State Society of Anesthesiologists, New York City, and sponsored by NATA—Network for Advancement of Transfusion Alternatives—and Abbott Laboratories.

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Special REPORT

CME ACCREDITED APRIL 2002

Issues in Fluid Volume Replacement

NEEDS STATEMENT

Aggressive intraoperative fluid replacement has been shown to improve surgical outcome. Studies have also revealed that some commonly used intravenous fluid replacement solutions can cause coagulopathy and impair renal function. Intraoperative administration of colloid solutions—with or without adjuvant crystalloid solutions—may improve surgical outcome by reducing rates of postoperative adverse events such as nausea, vomiting, and pain.

This monograph was produced to inform anesthesiologists about current thinking on the characteristics of commonly used intraoperative fluids.

ACCREDITATION AND CREDIT DESIGNATION STATEMENT

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Dannemiller Memorial Educational Foundation and McMahon Publishing Group. The Dannemiller Memorial Educational Foundation is accredited by the ACCME to provide continuing medical education for physicians.

The Dannemiller Memorial Educational Foundation designates this educational activity for a maximum of 1 hour in category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he or she actually spent in the educational activity.

INTENDED AUDIENCE

This activity is intended for anesthesiologists, as well as cardiothoracic and cardiovascular surgeons.

FACULTY

Aryeh Shander, MD, Chief, Department of Anesthesiology, Critical Care Medicine, Pain Management and Hyperbaric Medicine, Englewood Hospital and Medical Center, Englewood, N.J. Dr. Shander is also Associate Clinical Professor of Anesthesiology, Mount Sinai School of Medicine, New York City, and Executive Director, Society for the Advancement of Blood Management. Dr. Shander disclosed that he is a consultant and speaker for Abbott Labs, OBI, Amgen, Hemosol.

Jean-François Baron, MD, Professor of Anesthesiology, Department of Anesthesiology, Pitié-Salpêtrière Hospital, Paris, France. Dr. Baron disclosed that he has received honoraria for speaking engagements from Abbott Labs. As of January 2002, Dr. Baron works for Fresenius Kabi.

Elliott Bennett-Guerrero, MD, Florence Irving Assistant Professor, Director, Cardiothoracic Anesthesiology, Columbia University College of Physicians and Surgeons, New York, New York. Dr. Bennett-Guerrero disclosed that he has received honoraria for speaking engagements and an unrestricted educational research grant from Abbott Labs. Prior to 2000 he served as a consultant for and received research grants from BioTime.

Michael G. Mythen, MD, Portex Professor of Anaesthesia and Director, Centre for Anaesthesia, University College London; Clinical Director, Critical Care Medicine, University College London Hospitals, London, England. Prof. Mythen disclosed that he has received honoraria for speaking engagements and an unrestricted educational grant from Abbott. He has served as a consultant for and received research grants from BioTime. He has received speaking honoraria from Fresenius Kabi and a research grant from B. Braun.

OBJECTIVES

❶ Compare the use of colloids and crystalloids in volume resuscitation.
❷ Discuss evidence from clinical trials in fluid volume replacement.
❸ Explain the use of albumin in treating critically ill patients.
❹ Compare the physiologic effects of normal-saline-based vs. balanced-electrolyte-solution-based fluids.
❺ Explain the effects of volume resuscitation fluids on coagulation.

GOAL

To re-evaluate the most common fluid volume replacement strategies and their effects on outcome.

METHOD OF PARTICIPATION

This activity should take approximately 1 hour to complete. The participant should, in order, read the objectives and monograph, answer the 10-question, multiple-choice post-test, and complete the evaluation on page 8. The evaluation form provides each participant with the opportunity to comment on the quality of the instructional process, the perception of enhanced professional effectiveness, the perception of commercial bias, and his or her views on future educational needs. To receive credit for this activity, follow the instructions provided on the post-test. This credit will be valid through April 30, 2003. No credit will be given after that date.

Introduction

Can the colloid/crystalloid debate be resolved? Not today, but perhaps it can be reformulated. Maybe the question of colloid or crystalloid is not so important as questions of fluid vehicle, dosage, and timing of administration.

Studies discussed in this symposium show that the choice of fluid can have clinically and statistically significant effects on quality of recovery, particularly with regard to renal function and coagulation.

These were among the conclusions reached in presentations at "Issues in Volume Replacement," a satellite symposium held during the 2001 annual Postgraduate Assembly of the New York State Society of Anesthesiologists. The educational symposium was cosponsored by the Network for Advancement of Transfusion Alternatives (NATA) and Abbott Laboratories.

Crystalloid Therapy: Is It Time to Rethink?

The colloid/crystalloid debate has persisted since soon after Dr. Ringer developed the now famous Ringer's solution. Today there are no consistent, high-quality data indicating that either colloids or crystalloids are superior, if mortality is the criterion.

There have been a number of systematic reviews of studies comparing colloids and crystalloids. "These systematic reviews showed there is no difference between colloids and crystalloids," explained Michael G. Mythen, Portex Professor of Anaesthesia and Director of the Centre for Anaesthesia at University College London, and Clinical Director of Critical Care Medicine, University College London Hospitals, London, England.

Although serious students of this subject agree that there is no difference between colloids and crystalloids in terms of mortality, there is accumulating evidence of other clinically significant differences among fluids used for volume resuscitation.

More important than the question of colloid or crystalloid may be the question of fluid vehicle. "The electrolyte composition of the fluid administered and the dosage and timing of administration are probably far more important issues than the distinction between colloid and crystalloid," Dr. Mythen conjectured.

Duke Study of Pharmaceutical Practice Guidelines

Dr. Mythen related an experience from his days as an attending anesthesiologist at Duke University Medical Center in Durham, NC. "As part of an effort led by Dr. David Lubarsky to produce a set of pharmaceutical practice guidelines, I was charged with reviewing the evidence for colloid usage versus crystalloid usage and producing some guidelines. The fluid guidelines essentially suggested that we abandon colloids in favor of crystalloids."

After implementation of the guidelines,[1] the Duke team determined that there had been a reduction in the cost per case. From an economic perspective, the group's work paid dividends. "As a result of implementing the practice guidelines, we reduced the drug cost on average per case from $56 to $32," Dr. Mythen noted.

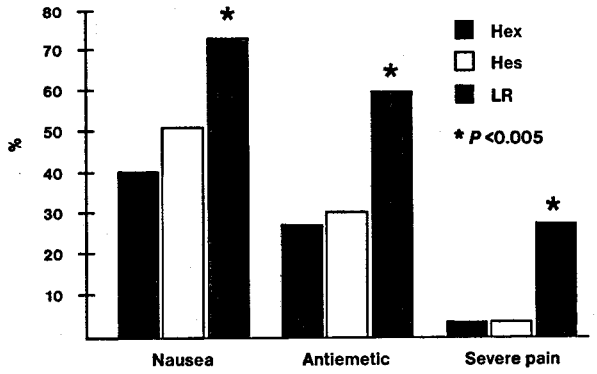

Figure 1. Postoperative nausea and pain.

Early on, implementation of the guidelines seemed to be having effects that were too good to be true: costs were down without any apparent reduction in the quality of patient care. "There were some rumblings that came from elsewhere in the institution," Dr. Mythen reported.

Unexpected Results

Later at Duke, when Dr. Mythen was an attending in the ICU, "one thing that we noticed there was that patients who came back to the ICU seemed to require secondary resuscitation because they had been crystalloid resuscitated."

"The acute pain team, then headed by T.J. Gan, MD, reported more edema-related problems in patients who had gone back to the floor," Dr. Mythen continued. "They also thought that the patients were experiencing more pain and a higher incidence of double vision. So there was this suggestion of a reduction in the quality of recovery in the patients."

Dr. Gan decided to study these apparent trends,[2] conducting a prospective, double-blind, randomized trial comparing 2 starch colloids with a crystalloid limb for patients undergoing major surgery.

A study conducted by Gan et al[3] looked at the efficacy and safety of 2 fluids for the treatment of blood loss during major noncardiac surgery. All patients (n=180 in 3 groups) received a background infusion of lactated Ringer's (LR). They were then randomized in a blinded fashion to receive boluses of 6% hydroxyethyl starch in a balanced electrolyte solution (Hex), 6% hydroxyethyl starch in normal saline (Hes), or all crystalloid in the form of LR.

"The bottom line here is that in this prospective, randomized study, T.J. Gan and his colleagues reported a statistically significant higher incidence of nausea, the use of rescue antiemetics, severe pain in these people, and periorbital edema and double vision in patients receiving crystalloid only. (See Figure 1.) So their anecdotal experiences were supported by this prospective, randomized, controlled trial," Dr. Mythen said.

Hyperchloremic Metabolic Acidosis

Another important question relates to the role of a fluid's vehicle on clinical outcomes. "Although we refer to 0.9% NaCl as 'normal saline,' it's not actually a very normal solution at all," Dr. Mythen explained. "It's relatively normal because it's iso-osmolar, but it's acidic in the bag and has quite a high chloride content. Remember that a normal plasma chloride is approximately 100 mmol/L, so 0.9% NaCl is a hyperchloremic solution."

In a study designed to investigate the effects of normal saline (NS) versus LR, Williams et al[4] enrolled 18 healthy volunteers. They gave approximately 50 mL/kg of either NS or LR to 18 healthy volunteers in a blind, crossover design.

"A remarkable feature was that healthy volunteers who received NS developed a very reproducible, previously described hyperchloremic metabolic acidosis as a result of the chloride administration," Dr. Mythen reported. "But also greater than 80% of them developed both subjective and objective CNS [central nervous system] changes and greater than 50% developed abdominal discomfort. (See Figure 2.)

"So this previously perceived to be benign phenomenon of hyperchloremic metabolic acidosis may not be that benign." The volunteers treated with LR experienced no CNS changes and much less abdominal discomfort.

"I could only find one other reference that tells you about clinical experiences with hyperchloremic metabolic acidosis, and that comes from ammonium chloride poisoning. So if you get out your old poisons book and look up 'ammonium chloride poisoning,' it produces a hyperchloremic metabolic acidosis, the same symptoms as the those experienced by the healthy volunteers who received saline in the Williams study—confusion, headache, nausea, and abdominal pain."

"If you are a colloid resuscitator, until the introduction of 6% hydroxyethyl starch in a balanced electrolyte and dextrose injection—Hex—you were a saline resuscitator," Dr. Mythen cautioned.

6% Hydroxyethyl Starch in a Balanced Electrolyte Solution vs Lactated Ringer's

Referring to a study conducted by himself and colleagues,[5] Dr. Mythen described a comparison of Hex, LR, NS, and Hes in elderly patients undergoing major surgery.

Forty-seven such patients were randomly allocated to 1 of 2 study groups. Patients in the balanced fluid group received an intraoperative fluid regimen that consisted of Hex and the crystalloid LR. Patients in the saline group were given Hes and the crystalloid NS. Postoperative chloride levels showed a larger increase in the saline group than the balanced fluid group (9.8 vs 3.3 mmol/L, P=0.0001). Postoperative standard base excess showed a larger decline in the saline group than the balanced fluid group (-5.5 vs -0.9 mmol/L, P=0.0001). Of patients in the saline group, approximately 67% developed postoperative hyperchloremic metabolic acidosis, compared with none in the balanced fluid group (P=0.0001). (See Figure 3.) In this study, the use of balanced crystalloid and colloid solutions in elderly surgical

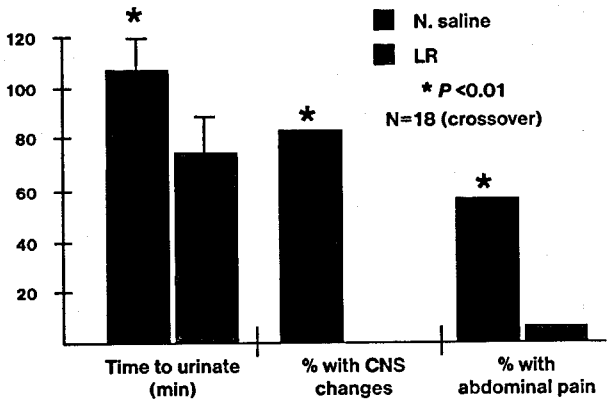

Figure 2. N. saline vs LR in healthy volunteers.

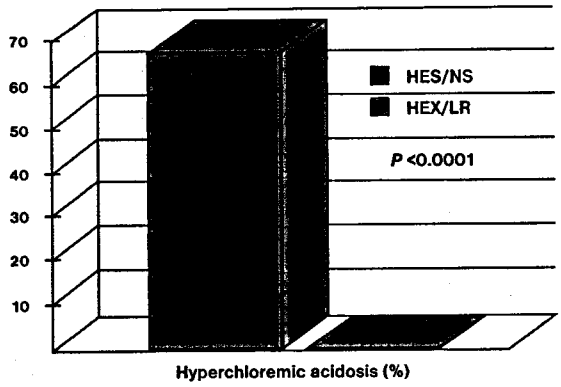

Figure 3. Hyperchloremic metabolic acidosis at end of surgery.

patients prevented the development of hyperchloremic metabolic acidosis and resulted in improved gastric mucosal perfusion when compared with saline-based solutions.

"Simply by switching the electrolyte solution of the colloid and the crystalloid, we were able to reduce the incidence of hyperchloremic metabolic acidosis at the end of surgery from over 65% to zero," Dr. Mythen explained.

Human Albumin—When Is It Appropriate?

Internationally, albumin has come to be used increasingly for fluid volume replacement. However, Jean-François Baron, MD, Professor of Anesthesiology in the Department of Anesthesiology at Pitié-Salpêtrière Hospital in Paris, France, presented evidence that the routine use of albumin in critically ill patients is not supported by published data and, worse, that it may increase mortality in critically ill patients.

The volume-expanding effects of albumin can vary significantly among patients and over time in a single patient. The theoretical volume-expanding power of albumin is 18 to 20 mL/g, or 400 mL for a 500-mL infusion of a 4% albumin solution, according to Dr. Baron's symposium notes. However, because of factors such as patient population,

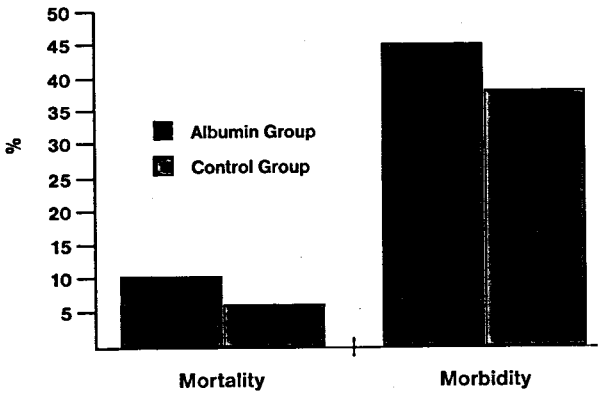

Figure 4. Results of albumin supplementation in the ICU. (Adapted from reference 10.)

hydration status, and endogenous albumin stores, the volume expansion properties of the drug vary. According to a study by Schwartzkopff et al,[6] 5 to 8 g of albumin is lost from the intravascular space every hour. Albumin leaks more quickly in normovolemic and hypoproteinic patients.

Albumin for Treatment of Hypoalbuminemia?

Albumin is commonly used to treat hypoalbuminemia in ICU patients.[7] "Its use, however, does not improve morbidity or mortality," according to Dr. Baron. He cited 2 studies supporting these claims.[8,9]

Albumin replacement therapy offers no benefit to hypoalbuminemic patients in the surgical ICU, according to a study by Golub et al.[10] (See Figure 4.) Patients (n=219) with circulating albumin concentrations of <3.0 g/dL upon admission were studied. The groups were well matched by age, sex, Acute Physiology and Chronic Health Evaluation II scores, and initial circulating albumin concentrations, according to the report. In this prospective, randomized study, patients treated with albumin (n=116) experienced a complication rate of 44% (*P*=0.22) versus just 36.9% in the nonsupplementation control group (n=103; *P*=0.22). There were no significant differences between the groups in the number of days spent receiving mechanical ventilation or in the tolerance to tube feedings.

"Routine supplemental administration of 25% albumin is expensive and offers no apparent outcome advantage and should be abandoned in the treatment of patients in the surgical ICU," the authors wrote.

According to the authors of a meta-analysis performed by the Cochrane collaboration, "There is no evidence that albumin administration reduces mortality in critically ill patients with hypovolemia, burns, or hypoalbuminemia and a strong suggestion that it may increase mortality. These data suggest that use of human albumin in critically ill patients should be urgently reviewed and that it should not be used outside the context of rigorously conducted randomized, controlled trials."[11] (See Figure 5.)

This meta-analysis reviewed 30 randomized trials that included 1,419 patients. The main outcome measure was mortality from all causes at the end of the follow-up period for each trial. In patients treated for hypovolemia, the relative risk of death after albumin administration was 1.46 (95% confidence interval [CI], 0.97-2.22). In patients treated for burns, the relative risk was 2.40 (1.11-5.19). In those treated for hypoalbuminemia, it was 1.69 (1.07-2.67). Pooled relative risk of death with albumin administration was 1.68 (1.26-2.23). Pooled difference in the risk of death with albumin was 6% (95% CI, 3% to 9%) with a fixed-effect model. "These data suggest that for every 17 critically ill patients treated with albumin, there is one additional death," the authors wrote.

"This study was widely criticized in letters to the editor published in the *BMJ*," Dr. Baron noted. "Criticisms mainly focused on the poor selection of studies–ie, the inclusion of studies restricted not only to albumin but also involving fractionation products of varying quality–and the use of mortality as a main study outcome measure."

A study conducted by Foley et al investigated the effects of albumin supplementation in critically ill patients (n=40).[8] The study was a prospective, randomized trial of 25% albumin administration in 40 hypoalbuminemic (serum albumin <25 g/L), critically ill patients. The treatment group (n=18) received 25% albumin supplementation to achieve and maintain serum albumin levels of 25 g/L or greater, while the nontreatment group (22 patients) received no concentrated albumin.

"There was no clinical benefit from albumin therapy when assessing mortality (39% vs 27%, treatment vs control) or major complication rate (89% vs 77% of patients)," the authors concluded. "There were also no significant differences in length of hospital stay, intensive care unit stay, ventilator dependence, or tolerance of enteral feeding, despite significant elevations of albumin in the treatment group. The costly use of exogenous albumin as treatment for hypoalbuminemia in this patient population does not appear to be justified."

Of importance is that the results published by the Cochrane Injuries Group and others questioning the benefit

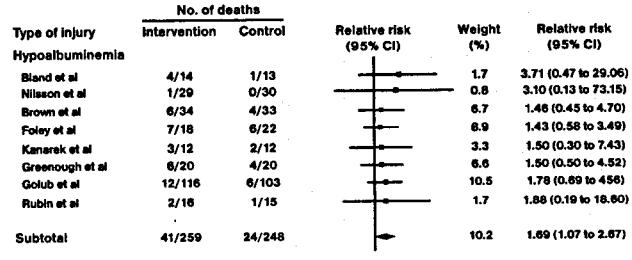

Figure 5. Systematic review of randomized, controlled trials of albumin administration in critically ill patients. (Adapted from reference 11.)

of albumin administration on some patients were not supported in a later meta-analysis conducted by Wilkes et al.[12] This study reviewed 55 trials involving surgery or trauma, burns, hypoalbuminemia, high-risk neonates, ascites, and other indications. The primary end point for this study was relative risk for death. Albumin administration did not significantly affect mortality in any category of indications. For all trials, the relative risk for death was 1.11 (95% CI, 0.95-1.28). Relative risk was lower among trials with blinding (0.73 [0.48 to 1.12]; n=7), mortality as an end point (1.00 [0.84-1.18]; n=17), no crossover (1.04 [0.89-1.22]; n=35), and 100 or more patients (0.94 [0.77-1.14]; n=10). In trials with 2 or more such attributes, relative risk was further reduced.[13]

"Overall, no effect of albumin on mortality was detected; any such effect may therefore be small," Wilkes et al wrote in conclusion. "This finding supports the safety of albumin. The influence of methodologic quality on relative risk for death suggests the need for further well-designed clinical trials."

Artificial Colloid Solutions—Hydroxyethyl Starches, Gelatins, and Dextrans

In this presentation, Dr. Mythen reviewed the agents commonly used for volume resuscitation. Artificial colloids or synthetic colloids are commonly referred to as a single entity. However, they can be divided into 3 major groups: hydroxyethyl starches, gelatins, and dextrans.

The most commonly used crystalloids in contemporary surgery are glucose 5%, NS, glucose saline, LR solution, compound sodium lactate, and Plasmalyte B. Among the most popular colloids used in surgery around the world are gelatin, dextran 70 in saline, Hes, and human albumin solutions.

"Most of us understand a colloid by its clinical definition as a substance that stays in the intravascular space when put there—even though that's not the truth of the matter—while a crystalloid is thought of as going beyond the intravascular space," Dr. Mythen noted. "Crystalloids tend to be defined in terms of pH, osmolality, and electrolyte composition."

A colloid is a homogeneous noncrystalline substance consisting of large molecules or ultramicroscopic particles of one substance dispersed through a second substance. The particles do not settle and cannot be separated out by ordinary filtering or centrifuging.

A key characteristic of the various colloids is polydispersity, which is determined by the size of the molecule. The larger the molecular size, the more prolonged the intravascular retention, but because there are fewer particles per unit volume, the result is less volume expansion.

"Now probably the most commonly used colloids in the world are the hydroxyethyl starches," Dr. Mythen noted. All currently available isotonic Hes solutions are formulated in 0.9% sodium chloride, with the exception of Hex.

"What's the bottom line?" Dr. Mythen asked. "Well—surprise, surprise—there is no difference, according to a meta-analysis or systematic review of any study that has looked at any colloid versus any other colloid in terms of mortality."

"If you look at the big picture," Dr. Mythen continued, "there would appear to be no clinically significant differences that allow you to choose between hydroxyethyl starches, gelatins, or dextrans. As for the colloid debate per se, time and dosage are probably much more important than which colloid. I'm increasingly convinced that formulation again may be more important than the colloid itself."

Volume Resuscitation in Major Surgery: Does the Choice of Fluid Matter?

Effect of Vehicle on Coagulation

By this point, symposium attendees had seen considerable evidence that the choice of fluid is not as important as the fluid vehicle. A number of studies strongly suggest that a chloride load impairs renal function and can lead to hyperchloremic metabolic acidosis. Dr. Bennett-Guerrero presented selections from the growing body of evidence that the type of vehicle in which a fluid is formulated can affect clinical end points, although the underlying mechanisms are not yet fully undertood.

Scheingraber et al examined the effects of changes in acid-base balance created by infusion of 0.9% NaCl. The dose-response study included 24 women undergoing major intra-abdominal gynecologic surgery who were given 30 mL/kg per hour of either an NS-based fluid or LR.[14] Patients randomized to the NS solution had a tendency toward lower urine output, the authors found. The saline infusion caused hyperchloremic metabolic acidosis. In addition, patients given the saline infusion had a tendency toward more bleeding than those in the LR group.

Major Surgery: Choice of Fluids Affects Blood Loss

A prospective, randomized, 2-center Phase III study comparing the safety and efficacy of 2 formulations of 6% hetastarch—Hes and Hex—compared efficacy and safety of the 2 solutions for the treatment of hypovolemia during major surgery.[3] Patients at one center had a blood sample drawn at the beginning and at the end of surgery for thromboelastographic (TEG) analysis. Hex was as effective as Hes for the treatment of hypovolemia. Patients received an average of 1,596 mL of Hex: 42% received >20 mL/kg up to a total of 5,000 mL. No patient received albumin. Hex-treated patients required less intraoperative calcium (4 mg vs 220 mg; P <0.05). In a subset analysis of patients receiving red blood cell transfusions (n=56; 47%), Hex-treated patients had a lower mean estimated blood loss (956 mL less; P=0.02) and were less likely to receive calcium supplementation (P=0.04). Patients receiving Hes demonstrated significant prolongation of time to onset of clot formation (based on TEG) not seen in the Hex patients (P <0.05). No Hex patient experienced a related serious adverse event, and there was no difference in the total number of adverse events between the 2 groups.

In a study by Waters et al,[15] patients undergoing aortic

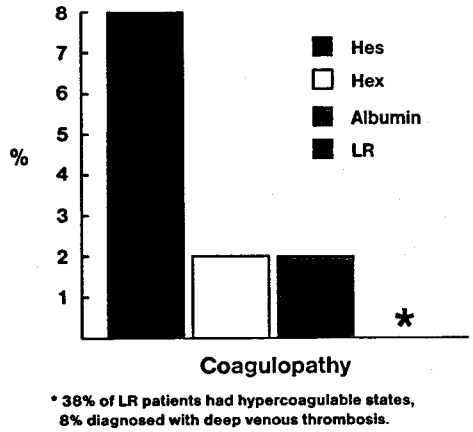

Figure 6. Comparison of postoperative coagulopathy.

reconstructive surgery were randomly assigned to receive LR solution (n=33) or NS (n=33) in a double-blind fashion. Anesthetic and fluid management were standardized. Multiple measures of outcome were monitored. The NS patients developed a hyperchloremic acidosis and received more bicarbonate therapy (30±62 mL in the NS group vs 4±16 mL in the LR group; mean ± SD), which was given if the base deficit was greater than -5 mEq/L. The NS patients also received a larger volume of platelet transfusion (478±302 mL in the NS group vs 223±24 mL in the LR group; mean ± SD). Patients in the NS group received significantly more blood products (P=0.02). There were no differences in duration of mechanical ventilation, ICU stay, hospital stay, or incidence of complications. When NS was used as the primary intraoperative volume resuscitation solution, significantly more acidosis was seen at the completion of surgery. This acidosis resulted in no apparent change in outcome but required larger amounts of bicarbonate to achieve predetermined measurements of base deficit and was associated with the increased use of blood products. Urine output was greater in patients who received NS, which could have been due to their having received a larger total volume of fluid.

"These changes should be considered when choosing fluids for surgical procedures involving extensive blood loss and requiring extensive fluid administration," the authors wrote. "Predominant use of 0.9% saline solution in major surgery has little impact on outcome as assessed by duration of mechanical ventilation, intensive care unit stay, hospital stay, and postoperative complications, but it does appear to be associated with increased perioperative blood loss."

Effects of Four Fluids in Major Cardiac Surgery

Dr. Bennett-Guerrero presented the findings of a recently completed randomized, blinded clinical trial conducted at Columbia University (unpublished). The study, of which he was lead investigator, included 200 patients undergoing coronary artery bypass graft and/or valvular heart surgery. Patients who were administered Hes exhibited impaired renal function and impaired coagulation after surgery compared with those given Hex.

Patients in the study were randomized to receive 1 of 4 fluids for intraoperative volume replacement: 1) 5% albumin in an NS-based vehicle, 2) LR, 3) Hes, and 4) Hex. Hes and Hex contain the same starch, Dr. Bennett-Guerrero noted.

"This trial was investigator initiated," Dr. Bennett-Guerrero stated. "It wasn't sponsored by any pharmaceutical company."

Coagulation Results

Describing the coagulation results, Dr. Bennett-Guerrero noted that the following outcomes were measured: percentage of patients transfused and the volumes of allogeneic packed red blood cells (pRBC), platelets, and fresh frozen plasma (FFP) administered in the perioperative period (defined as during surgery plus 24 hours after surgery). In addition to these tests, TEG was performed in study patients immediately before induction, after the administration of protamine, and on postoperative day 1.

Patients randomized to a fluid with an NS-based vehicle showed evidence of increased bleeding. For example, in the perioperative period, Hes patients received a median 4 units of pRBC (interquartile range [IQR], 2-6), while Hex and albumin patients received 2 units (IQR, 0-2). Similarly, in the same period, Hes patients received transfusions of a median 3 units of FFP (IQR, 0-6) and 6 units of platelets (IQR, 0-9), compared with 0 units of FFP (IQR, 0-4.5) and 0 units of platelets (IQR, 0-6) for Hex patients and 0 units of FFP (IQR, 0-4) and 0 units of platelets (IQR, 0-6) for patients receiving albumin.

The proportion of patients receiving platelets or FFP perioperatively differed significantly between groups (P <0.0001): Hes, 69%; Hex, 47%; albumin, 42%; and LR, 26%. Overall, albumin and Hex patients had similar outcomes with regard to coagulation, while Hes patients showed significant coagulopathy. (See Figure 6.)

In addition, patients receiving the NS-based starch were more likely to return to the OR for reoperation because of coagulopathy—Hes, 8%; Hex, 2%; albumin, 2%; and LR, 0%—although this difference was not statistically significant.

"Of interest was the fact that 38% of patients in the lactated Ringer's group had evidence of a hypercoagulable state postoperatively, and 8% of patients in the lactated Ringer's group were diagnosed with a deep venous thrombosis," Dr. Bennett-Guerrero remarked.

The study further showed that patients given starch-based fluids (either Hes or Hex) had less edema, less pain, less antiemetic use, and faster return of bowel function (all P <0.001) than those given albumin or LR.

"I think we're not going to see a lot of studies that demonstrate an impact of fluid vehicle type on mortality," Dr. Bennett-Guerrero conjectured. "There is growing evidence based on these 2 studies that giving large volumes of crystalloids can have deleterious effects. One of these effects is edema.

"With regard to periorbital edema, we saw more edema in patients receiving LR than in those receiving starches. There is almost as much edema in patients receiving albumin as LR. Really, this isn't so surprising for those who are familiar with the literature. In patients with capillary leak syndrome, for example, during cardiac surgery we know that a lot of this albumin is leaking into the extravascular space."

With regard to perioperative pain, there was no difference in preoperative Visual Analogue Scale scores. Postoperatively, as Gan et al had found at Duke, patients receiving crystalloid only or albumin experienced more pain than those receiving starches.

Increased PONV Seen With Crystalloids

The study revealed more nausea and increased use of antiemetics, as well as longer times to return to solid food, in patients receiving LR or albumin than in those receiving starches. "These are statistically significant differences," Dr. Bennett-Guerrero noted.

With regard to pulmonary function, the PaO_2/FiO_2 ratio was not different between the albumin- and the LR-treated patients. "So despite the fact that many people think that you should give albumin to patients rather than LR because you're going to have drier lungs and better pulmonary function," Dr. Bennett-Guerrero remarked, "there is very little evidence to support this in the literature. In our study there was not even a trend towards any benefit related to pulmonary function in patients administered the albumin.

"In summary, I think that the administration of NS-based fluids can definitely impair renal function. I want to emphasize that this is in major surgery in patients who are at higher risk for renal dysfunction. If you're doing a case where you're giving 1 L of fluid or 2 L of fluid, it probably doesn't matter what you give. Our data suggest that Hes can cause derangements in coagulation. Based on all the studies that have been done, Hex is more similar to 5% albumin with regard to coagulation."

Conclusion

Based on the evidence presented at this NATA symposium, it is difficult to avoid the conclusion that there are still many unanswered questions with regard to perioperative fluid management.

The debate over colloids and crystalloids for perioperative fluid replacement has been inappropriately focused. Recent studies make it clear that the fluid vehicle may be as important as the choice of fluid itself. These studies also suggest that administration of NS-based fluids—including albumin—is associated with a decreased quality of recovery that may be related to renal dysfunction and coagulopathy.

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Questions for CME Credit

Choose the single-letter response that best answers the question or completes the sentence.

1. **After implementation of pharmaceutical practice guidelines at Duke, Gan et al found _____ in patients who received Hes.**
   a. significantly higher rates of nausea and use of antiemetics
   b. significantly greater incidence of severe pain
   c. increased incidence of periorbital edema and double vision
   d. all of the above
2. **In the study by Williams et al, most volunteers who received NS experienced:**
   a. hyperchloremic metabolic acidosis and CNS changes
   b. hyperchloremic metabolic acidosis without CNS changes
   c. CNS changes without hyperchloremic metabolic acidosis
   d. none of the above
3. **According to Dr. Mythen, symptoms of hyperchloremic metabolic acidosis include:**
   a. confusion
   b. nausea and vomiting
   c. pain
   d. all of the above
4. **In the study of elderly patients for major surgery, ___% of those in the NS group developed hyperchloremic metabolic acidosis, compared with ___ in the Hex group.**
   a. 0%, 67%
   b. 6.7%, 0%
   c. 67%, 0%
   d. 0%, 6.7%

5. **In the investigation by Golub et al into the effects of albumin supplementation in critically ill hypoalbuminemic patients, those treated with albumin experienced a 44% complication rate.**
   a. True
   b. False

6. **According to the meta-analysis performed by the Cochrane Collaboration, patients treated with albumin for ____ were at a relative risk of death of ____.**
   a. burns, 2.40
   b. hypoalbuminemia, 1.69
   c. hypovolemia, 1.46
   d. all of the above

7. **According to the study by Foley et al of the effects of albumin supplementation in critically ill patients, mortality was ___ in the albumin group and ___ in the control group.**
   a. 27%, 39%
   b. 89%, 77%
   c. 39%, 27%
   d. 77%, 89%

8. **According to results of the study by Scheingraber et al, Hes patients experienced a significant prolongation of time to clot formation, according to TEG.**
   a. True
   b. False

9. **In patients undergoing aortic reconstructive surgery, patients who received NS also ___ than those receiving LR.**
   a. received more blood products
   b. experienced more hyperchloremic metabolic acidosis
   c. received a larger volume of platelet transfusion
   d. all of the above

10. **In the study conducted at Columbia by Dr. Bennett-Guerrero and others, _____ of patients receiving Hes returned to the OR for reoperation because of coagulopathy.**
    a. 2%
    b. 8%
    c. 0%
    d. 18%

CME Post-test

Issues in Fluid Volume Replacement
–Released April 2002–

If you desire CME credit for this activity, circle the letter below that corresponds with each of your answers to the questions listed on pages 7 and 8. Complete the evaluation form below. The evaluation form and the post-test must be filled out completely for you to receive credit. Please print clearly. This credit is valid through April 30, 2003. No credit will be given after this date. Enclose a check for $15.00 payable to DMEF/IFVR. Mail to the address below:

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8.	a	b		
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10.	a	b	c	d

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B. communicate with patients.
a. Strongly agree b. Agree c. Disagree d. Strongly disagree
C. manage my medical practice.
a. Strongly agree b. Agree c. Disagree d. Strongly disagree
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Executive Summary Reference #4

Hextend® is a safe alternative to 5% human albumin for patients undergoing elective cardiac surgery

(1 page)

October 16, 2001
9:00:00 AM - 11:00:00 AM
Morial Convention Center, Room C

Hextend® Is a Safe Alternative to 5% Human Albumin for Patients Undergoing Elective Cardiac Surgery

Kenneth C. *Petroni*, M.D.; Richard Green, M.D.; Sean Birmingham, M.D.

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INTRODUCTION: Colloid solutions such as hetastarch and human albumin are frequently used as perioperative intravascular volume expanders. In patients undergoing cardiac surgery, the rationale for the use of colloids is the reported decrease in perioperative patient weight gain and improvement in postoperative pulmonary function secondary to the favorable oncotic properties of these solutions (1). Because the use of hetastarch has been associated with bleeding abnormalities in non-cardiac surgery populations, its use in patients undergoing cardiac surgery has been controversial. Hextend®, a new plasma volume expander containing 6% hetastarch in a lactated electrolyte solution, has not been reported to have any adverse effects on the coagulation system and its use in the cardiac surgery population has not been studied. Thromboelastography (TEG) is an established bedside monitor of perioperative coagulation function with an extensive history of use in the cardiac surgery population. Using TEG and clinical data, the purpose of this study is to determine whether Hextend® is a safe alternative to 5% human albumin for patients undergoing cardiopulmonary bypass (CPB) surgery.
METHODS: After IRB approval and written informed consent, 28 patients scheduled for elective cardiac surgery requiring cardiopulmonary bypass were randomized to receive either 5% human albumin in lactated Ringer's solution or Hextend® as their intraoperative and postoperative volume expander for up to 24 hours post-surgery. Patients scheduled for redo procedures, on any anticoagulation therapy, or with any history of renal or hepatic insufficiency were excluded. Patient characteristics, hemodynamic variables, laboratory data, TEG data, chest tube output every four hours, and blood product usage were recorded preoperatively, post-protamine intraoperatively, and on post-op day #1.
RESULTS: Fourteen patients were randomized to each group. Groups were evenly matched by age, sex, total CPB time and total colloid transfused. Preoperative TEG data and hematocrit were similar in both groups. There was no statistical difference in TEG data (r time, k time, maximum amplitude and coagulation index) intraoperatively and on POD #1. In addition, chest tube output was not statistically different in any of the 4 hour recorded intervals. There was no difference between pre and post-op hematocrits or blood product usage. CONCLUSION: Our results indicate that Hextend® has no adverse effects on the coagulation system and appears to be a safe and reasonable alternative to 5% human albumin for perioperative intravascular volume expansion in patients undergoing elective cardiac surgery.
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Anesthesiology 2001; 95:A198

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Executive Summary Reference #5

A prospective randomized comparison thromboelastographic profile in patients receiving lactated Ringer's solution, 6% hetastarch in saline during major surgery

(6 pages)

A Prospective Randomized Comparison of Thromboelastographic Coagulation Profile in Patients Receiving Lactated Ringer's Solution, 6% Hetastarch in a Balanced-Saline Vehicle, or 6% Hetastarch in Saline During Major Surgery

G. Martin, MB, FRCA, E. Bennett-Guerrero, MD, H. Wakeling, MB, FRCA, M. G. Mythen, MD, H. El-Moalem, PhD, K. Robertson, MD, D. Kucmeroski, BS, and T. J. Gan, MB, FRCA

Objectives: To compare the effects of lactated Ringer's solution (LR), 6% hetastarch in a balanced-saline vehicle (HS-BS), and 6% hetastarch in normal saline (HS-NS) on coagulation using thromboelastography.

Design: Prospective, randomized double-blinded evaluation of previously published clinical trial.

Setting: Tertiary-care medical center.

Participants: Patients undergoing elective noncardiac surgery with an anticipated blood loss >500 mL. A total of 90 patients were enrolled with 30 patients in each group.

Interventions: Patients received a standardized anesthetic. LR, HS-BS, and HS-NS were administered intraoperatively based on a fluid administration algorithm. Hemodynamic targets included maintenance of arterial blood pressure, heart rate, and urine output within a predefined range.

Measurements and Main Results: Thromboelastography variables for r time, k time, maximum amplitude, and α angle (mean ± SD) were recorded at induction of anesthesia, at the end of surgery, and 24 hours postoperatively. Patients in the LR group showed a state of hypercoagulation at the end of surgery with a reduction ($p < 0.005$) in r time (−3.8 ± 6.7 mm) and k time (−1.7 ± 2.5 mm). This state of hypercoagulation continued into the postoperative period. Patients in the HS-NS group showed a state of hypocoagulation with an increase ($p < 0.05$) in r time (+6.2 ± 8.5 mm) and k time (+1.7 ± 3.9 mm) and a reduction in maximum amplitude (−8.0 ± 9.8 mm) at the end of surgery. This state of hypocoagulation was reduced in the postoperative period. Patients in the HS-BS group showed no significant changes in coagulation status at end of surgery with the smallest changes in r time (−0.3 ± 4.1 mm), k time (+0.1 ± 3.1 mm), maximum amplitude (−5.4 ± 12.3 mm), and α angle (0.3 ± 12.5°).

Conclusion: LR-treated patients exhibited a hypercoagulative profile that persisted into the postoperative period. HS-BS administration was associated with a lesser change in the coagulation profile compared with HS-NS, which was associated with a hypocoagulative state.

KEY WORDS: colloid, crystalloid, hemostasis, 6% hetastarch, thromboelastography, coagulation, surgery

COAGULATION DISTURBANCES are deleterious to patients having any major surgery including cardiac[1] and noncardiac procedures.[2,3] Hypocoagulation can lead to bleeding, the administration of blood products, and return to the operating room for reexploration. At the other extreme, hypercoagulation may be a cause for many thromboembolic and graft occlusion complications observed after cardiac surgery,[4,5] vascular surgery,[6,7] and other types of noncardiac surgery.[8-11]

In a prospective, randomized double-blinded trial of patients undergoing major elective surgery, the effect of lactated Ringer's solution (LR), 6% hetastarch in a balanced-saline vehicle (HS-BS) (Hextend), and 6% hetastarch in normal saline (HS-NS) (Hespan) on coagulation as determined by thromboelastography was compared. This was an investigator-initiated evaluation of a previous Food and Drug Administration–guided phase III parent study examining the efficacy of HS-BS versus HS-NS.[12] The sole objective of this evaluation was to assess the effects of different fluids on the coagulation profile as determined by thromboelastography. A third arm of LR was added to this evaluation to assess the effect of the commonly used crystalloid LR. The new study also included a third time point to test whether the coagulation changes continue into the postoperative period.

METHODS

Institutional review board approval and written informed patient consent were obtained. Adult patients with an American Society of Anesthesiologists physical status 1 through 3 were enrolled into this double-blind prospective study. Patients undergoing major elective noncardiac surgery with an anticipated blood loss >500 mL were approached at Duke University Medical Center. Patients with coagulopathy, significant hepatic or renal dysfunction, congestive heart failure; patients who had received an investigational drug within the last 30 days; and patients with known hypersensitivity to hydroxyethyl starches were excluded.

The anesthetic protocol used during this study was similar to that used in a previous study at this institution.[12] Before the start of anesthesia, all patients received an intravenous bolus of 7 mL/kg of LR solution, followed by an intravenous infusion at a rate of 5 mL/kg/h throughout the surgery. Anesthesia was induced with thiopental and maintained with a balanced inhalation technique incorporating isoflurane, nitrous oxide, and oxygen with neuromuscular blockade supplied by vecuronium. Anesthesia was maintained as judged by standard clinical criteria. Blood and blood product usage, types and volumes of all fluids administered intraoperatively, and an estimation of blood loss were recorded.

The placement of an epidural catheter for postoperative pain relief was not prohibited, but regional anesthesia was not used intraoperatively. The only local anesthetic used perioperatively was a 3-mL test dose consisting of lidocaine 1.5% with 1: 200,000 epinephrine, administered to ensure correct placement of the epidural catheter and to prevent hemodynamic alterations, which may affect fluid and pharmacologic management.

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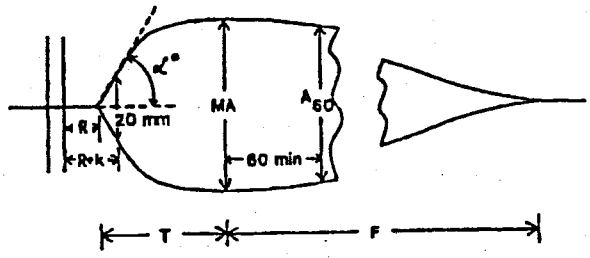

Fig 1. A normal thromboelastography trace. r time is measured from placing the sample in the cuvette until the tracing amplitude reaches 2 mm (normal range, 19 to 28 mm). k time is measured from the r time to the point where the amplitude of the tracing reaches 20 mm (normal range, 8 to 13 mm). α angle (α°) is the angle formed by the slope of the thromboelastography tracing from the r to the k value (normal range, 29° to 43°). Maximum amplitude (MA) is the greatest amplitude on the thromboelastography trace (normal range, 48 to 60 mm).[12]

Thromboelastography enables a global assessment of hemostatic function, taking into account the interaction of platelets with the protein coagulation cascade from the time of the initial platelet-fibrin interaction, through platelet aggregation, clot strengthening, and fibrin cross-linkage to eventual clot lysis. Patients had a blood sample drawn before induction, at the end of the surgical procedure, and 24 hours postoperatively for thromboelastography analysis. The sample was transferred within 4 minutes to prewarmed cuvettes of a thromboelastography device (TEG; Haemoscope Corp, Skokie, IL). All thromboelastography tests were performed in duplicate. A piston is suspended in the blood, and as coagulation proceeds, fibrin strands form between the walls of the cuvette and the piston. The piston becomes increasingly coupled to the motion of the cuvette; the shearing elasticity of the evolving blood clot is detected to yield the thromboelastography trace. Parameters recorded included r time (normal range, 19 to 28 mm), which denotes the rate of initial fibrin formation and is functionally related to plasma coagulation factors, and k time (normal range, 8 to 13 mm), which represents the time it takes for a fixed degree of viscoelasticity to be achieved by the forming clot. The k time is affected by the activity of the intrinsic coagulation factors, fibrinogen and platelets. Maximum amplitude (normal range, 48 to 60 mm) is a reflection of the absolute strength of the fibrin clot and can be altered by qualitative and quantitative platelet abnormalities. α angle (normal range, 29° to 43°) denotes the rate at which a clot is formed. A tracing of a normal thromboelastography trace is depicted in Fig 1. F1

In this double-blind study, patients were randomized to receive LR, HS-BS, or HS-NS for the treatment of hypovolemia according to a fluid management algorithm as previously reported (Fig 2).[12] Hextend is a new plasma volume expander containing 6% hetastarch (mean molecular weight, 550 kD), balanced electrolytes (Na^+, K^+, Ca^{++}, Mg^{++}, and Cl^-), lactated buffer, and physiologic levels of glucose (90 mg/dL). Hespan, in contrast to Hextend, consists of 6% hetastarch in 0.9% saline without added electrolytes. Based on this algorithm, hemodynamic targets included maintenance of arterial blood pressure, heart rate, and urine output within a predefined range. Blood products (platelets, fresh frozen plasma, cryoprecipitate, or fibrinogen) were administered when clinically indicated and supported by the laboratory evidence of abnormal coagulation: platelet count, <100,000/μL; prothrombin time, >1.5 times control; activated partial thromboplastin time, >1.5 times control; and fibrinogen, <100 mg/dL. F2

Based on pilot data, power calculation revealed that 30 patients per group were adequate to determine a 25% difference in r time with $\alpha = 0.05$ and $\beta = 0.2$. Data were analyzed using the Kruskal-Wallis, Fisher exact test, and analysis of variance test as appropriate. Results are presented as mean ± SD or median (interquartile range). A p value < 0.05 was considered statistically significant.

RESULTS

Ninety patients were enrolled overall with 30 patients in each group. The demographic data for the 3 groups were similar (Table 1). There was no statistically significant difference in the hematocrit and electrolytes between the 3 groups at baseline and end of surgery (Table 2). The previous study reported the thromboelastography data for the 2 colloid groups at baseline and end of surgery.[12] This study reports the thromboelastography changes at baseline, end of surgery, and postoperative day 1 for LR, HS-BS, and HS-NS groups. T1 T2

The mean changes in r and k time, maximum amplitude, and α angle for the LR, HS-BS, and HS-NS groups are shown in Fig 3. The results are given as mean change ± SD. LR showed a state of hypercoagulation at the end of surgery compared with baseline with a reduction ($p < 0.001$) in r (−3.7 ± 6.7 mm) and k (−1.7 ± 2.5 mm) time. This state of hypercoagulation continued up to postoperative day1 with a continued decrease ($p < 0.003$) in r (−8.8 ± 8.6 mm) and k (−2.6 ± 3.8 mm) time and an increase in α angle (+11.3 ± 13.9°) compared with baseline. HS-NS showed a state of hypocoagulation with an increase ($p < 0.05$) in r (+6.2 ± 8.5 mm) and k (+1.7 ± 3.9 mm) time and a reduction in maximum amplitude (−8.0 ± 9.8) at the end of surgery compared with baseline. No difference in thromboelastography variables was seen between postoperative day 1 and baseline. HS-BS showed no significant disturbance in coagulation at the end of surgery compared with baseline with the smallest changes in r (−0.3 ± 4.1 mm) and k (+0.1 ± 3.1 mm) time, maximum amplitude (−5.4 ± 12.3 mm), and α angle (+0.3 ± 12.5°). In the postoperative period up to postoperative day 1, HS-BS showed a degree of hypercoagulation with a change ($p < 0.0001$) in r time (−7.0 ± 8.2 mm) compared with baseline. There was no difference in intraoperative blood loss, red blood cells, or blood product utilization between the 3 groups. (Table 2) F3

DISCUSSION

In contrast to the previous study,[12] this study reports the effect of LR on thromboelastography and added an additional time point at 24 hours postoperatively to assess how thromboelastography variables change in the early postoperative period. Some of the major postoperative complications that occur, such as hemostatic disorders, deep vein thrombosis, and pulmonary embolism, may be related to the use of different types of fluids intraoperatively.[8,13,14] By adding this third time point, the effects of LR, HS-BS, and HS-NS on coagulation can be assessed at 24 hours postoperatively.

The administration of LR was associated with a hypercoagulable state with a reduction in r and k time and an increase in maximum amplitude. This hypercoagulable state continued into the postoperative period up to postoperative day 1. HS-NS treatment was associated with a hypocoagulable state with prolongation of the r and k times and a reduction in maximum amplitude. This hypocoagulable abnormality was normalized by day 1 postoperatively. HS-BS showed a better coagulation

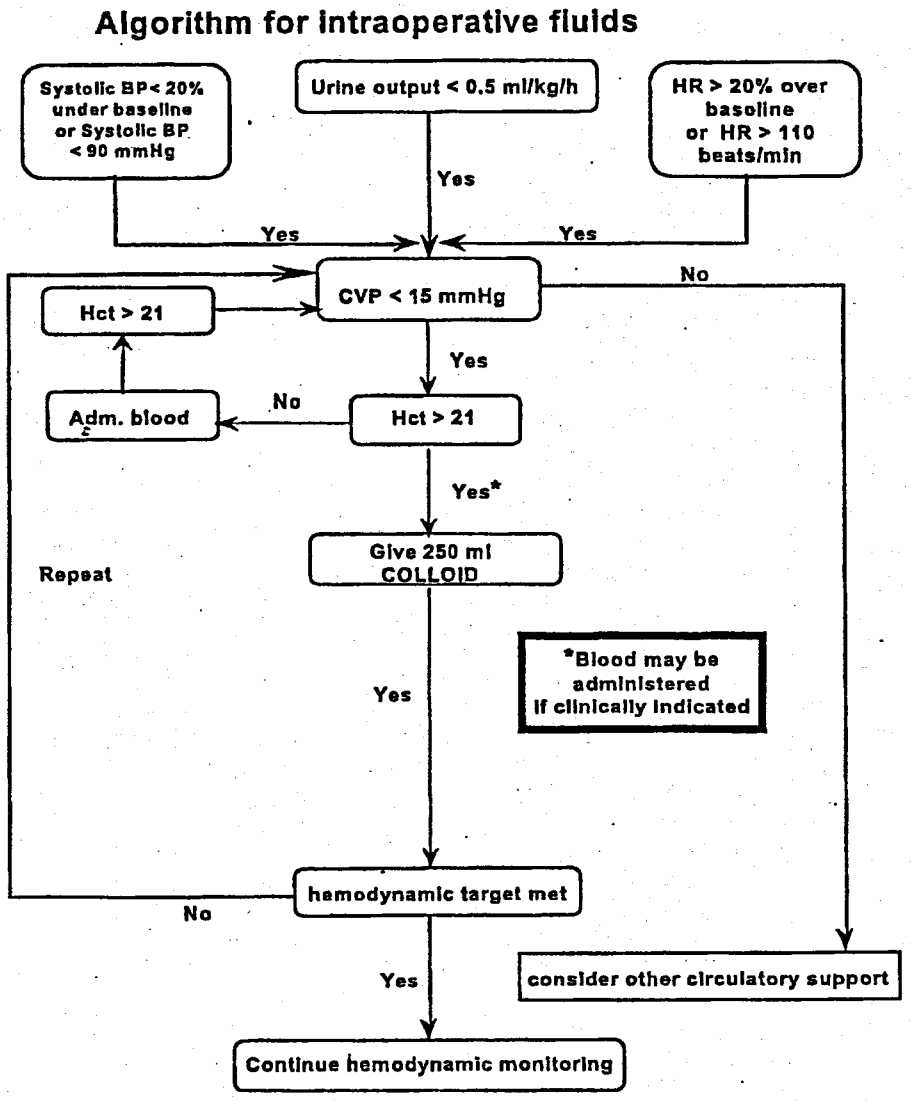

Fig 2. Algorithm for intraoperative colloid and crystalloid administration. BP, blood pressure; HR, heart rate; Hct, hematocrit; CVP, central venous pressure.[12]

profile compared with HS-NS or LR when used intraoperatively to treat hypovolemia. The thromboelastography profiles in HS-BS-treated patients showed the least change at the end of surgery. At postoperative day 1, HS-BS-treated patients exhibited an element of hypercoagulation as shown by a decrease in r time (Fig 3A and B).

The administration of LR in this study was associated with a procoagulant effect at the end of surgery and postoperative day 1 (Fig 3A and B). It is possible to speculate that this procoagulant effect may lead to an increased incidence of side effects, such as deep vein thrombosis and pulmonary embolism. These results are compatible with previous studies that showed this procoagulant effect of crystalloids *in vitro*[15,16] and *in vivo*.[8,17] Janvrin et al[8] not only showed a procoagulant effect because of hemodilution with crystalloid, but also an increased risk of deep vein thrombosis.[8] Patients who received normal saline had a 30% incidence of deep vein thrombosis, but only a 7% incidence was observed in patients who had a restricted fluid regimen. All these previous studies assessed the effect of saline solutions and not LR on coagulation. These findings of a hypocoagulant state in LR-treated patients suggest that this putative procoagulant state may be due to crystalloids regardless of their formulation.

This study also has shown that this procoagulant effect continues at least until 24 hours postoperatively (Fig 3A and B). The authors can only surmise on the cause of this state of hypercoagulation. The procoagulant state may predominate at moderate degrees of hemodilution. With increasing hemodilution, the procoagulant mechanisms may become increasingly affected resulting in hypocoagulation. Another possible mechanism by which crystalloids cause this procoagulant effect may be due to the rapid loss of the fluid from the intravascular space

Table 1. Demographic Data

	6% Hetastarch in Normal Saline (n = 30)	6% Hetastarch in Balanced Saline (n = 30)	Lactated Ringer's Solution (n = 30)
Age (y)	58 ± 11	59 ± 8	58 ± 8
Weight (kg)	79.3 ± 24.5	79.1 ± 16.8	82.8 ± 21.3
Height (cm)	168.5 ± 8.0	167.9 ± 15.9	173 ± 9.2
ASA			
1	2	1	1
2	13	15	14
3	15	14	15
Surgical type			
Gynecology	11	10	5
Urology	11	11	14
General	8	9	11

NOTE. Data are either mean ± SD or number of patients.
Abbreviation: ASA, American Society of Anesthesiologists.

into the interstitial fluid, which results in hemoconcentration of coagulation factors and other blood elements. The finding that LR-treated and HS-BS-treated patients exhibited a degree of hypercoagulation in the first 24 hours postoperatively may be related to the inhibition of the fibrinolytic system that can occur in major abdominal and orthopedic surgery postoperatively.[18-20] This phenomenon has been described as fibrinolytic shutdown and has been attributed to an imbalance between tissue-type plasminogen activator and plasminogen activator inhibitor that occurs postoperatively.

HS-NS is a commonly used colloid in the United States. This study showed a hypocoagulant effect of HS-NS at end of surgery compared with baseline. Decreases in factor VIII, fibrinogen, and von Willebrand's factor and increases in prothrombin time, partial thromboplastin time, and bleeding time[13,14,21-23] are potential mechanisms for HS-NS-induced hypocoagulation.[24-27] In a literature review of the last 30 years by Warren and Durieux[28] in which 18 clinical studies were included, they concluded that there was insufficient evidence from adequately controlled trials to address the question of whether the administration of HS-NS results in more clinically significant bleeding. The effects may be independent of the dose given. These investigators believed that it was difficult to recommend a maximum safe dosage because patients' responses were variable. The package insert for HS-NS does not specify a maximum safe dosage. By 24 hours postoperatively, the thromboelastography variables in HS-NS-treated patients had returned to baseline, suggesting that there may be no long-lasting hypocoagulant effect afforded to HS-NS.

HS-BS may have a minimal effect on hemostasis. In an *in vitro* study, Bick[29] serially diluted normal plasma samples with HS-BS or saline. HS-BS had no adverse effect on prothrombin time, partial thromboplastin time, factor X, fibrinogen levels, and factor VIII complex and rendered the same effect as dilution of plasma in saline. At all levels of dilutions with HS-BS, there was less prolongation of the prothrombin and partial thromboplastin times and smaller decreases in factor X, fibrinogen, and factor VIII complex levels. In this study, HS-BS compared with HS-NS and LR had a minimal effect on coagulation as assessed by thromboelastography at the end of surgery compared with baseline. This finding is in agreement with another study at this institution, which showed a statistically significant reduction in blood loss intraoperatively when comparing HS-BS, HS-NS, and LR.[30]

There are several possible mechanisms that could account for the observed differences in coagulation profiles between HS-BS and HS-NS. HS-BS, in contrast to HS-NS, is formulated in a balanced electrolyte solution including the presence of calcium (5 mEq/L). Calcium plays an important part not only in platelet activation, but also in the coagulation cascade. It is conceivable that the administration of larger volumes of HS-NS might be associated with hypocalcemia and impaired coagulation. Another possible explanation may lie in the difference in electrolyte composition. The level of chloride in HS-BS is 124 mEq/L versus 154 mEq/L in HS-NS. Large volumes of saline with its nonphysiologic levels of chloride have been associated with the development of a hyperchloremic acidosis. In a study by Scheingraber et al,[31] the rapid infusion of 0.9% saline but not LR caused a metabolic acidosis with hyperchloremic acidosis. There have been many reports of the association between the development of hyperchloremic acidosis and rapid saline infusion, leading to the use of the term *dilutional acidosis*.[32,33] The lower levels of chloride in HS-BS compared with HS-NS may account for these putative differences in coagulation profile through some yet undetermined mechanism.

Table 2. Intraoperative Fluids, Estimated Blood Loss, Hematocrit, and Blood and Blood Products Administration

	6% Hetastarch in Normal Saline (n = 30)	6% Hetastarch in Balanced Saline (n = 30)	Lactated Ringer's Solution (n = 30)
Volume of study fluid (mL)	1,301 ± 1,079	1,448 ± 759	5,946 ± 1,909*
Lactated Ringer's Solution (mL)	3,050 ± 1,531	3,242 ± 1,308	5,946 ± 1,909*
Hematocrit (%)			
Baseline	33.7 ± 6.03	35.4 ± 4.68	36.6 ± 3.60
End of surgery	28.9 ± 5.52	30.5 ± 3.92	32.1 ± 4.40
Red blood cells (mL)	348 ± 801	281 ± 488	303 ± 518
Fresh frozen plasma (mL)	68 ± 254	58 ± 187	37 ± 149
Platelets (mL)	16 ± 86	7 ± 39	0
Cryoprecipitate (mL)	3 ± 18	0	0
Estimated blood loss (mL)	550 (175–1,250)	388 (200–1,000)	725 (350–1,700)

AQ: 3

NOTE. Values are mean ± SD or median (IQR).
*$p < 0.05$ hetastarch in normal saline, hetastarch in balanced saline versus lactated Ringer's solution group.

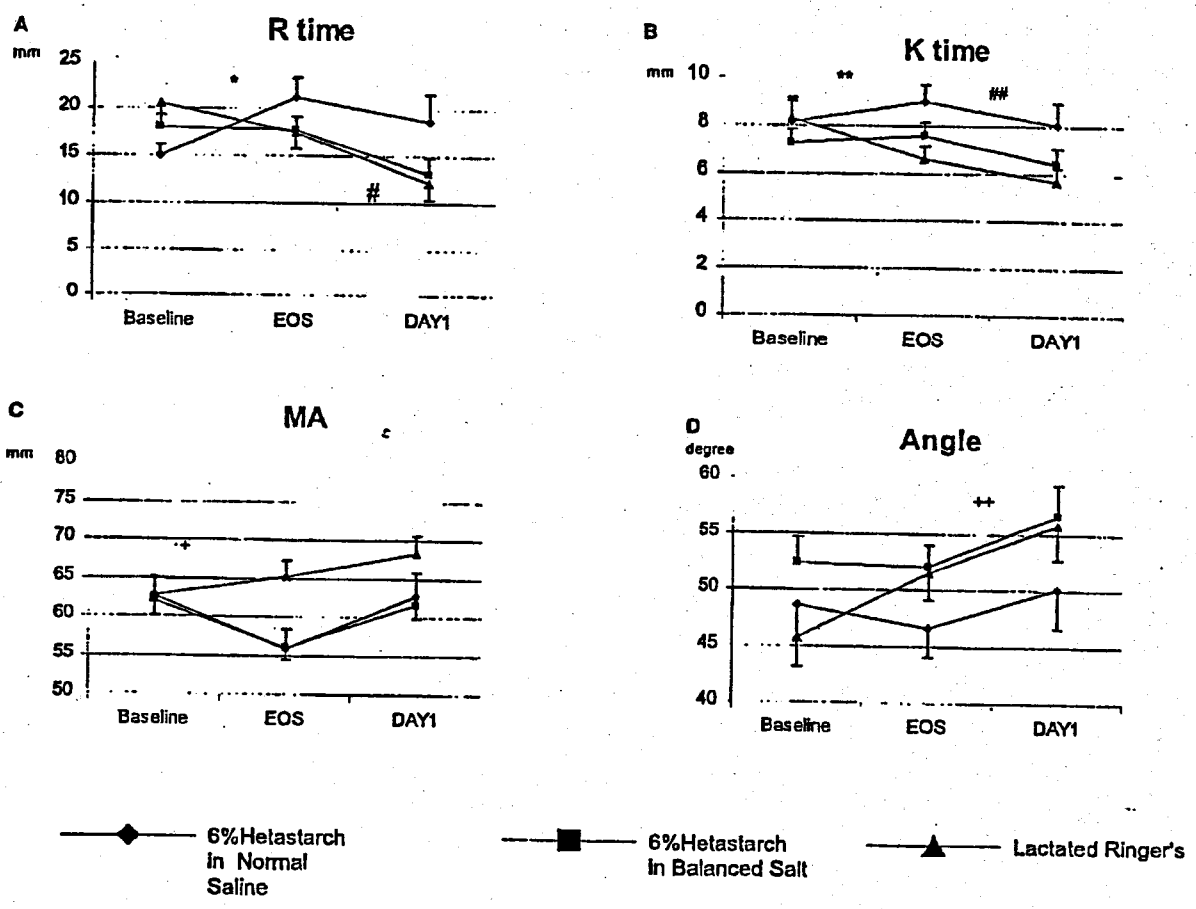

Fig 3. Change in r time, k time, maximum amplitude and α angle for HS-BS, HS-NS, and LR at baseline, EOS (end of surgery) and day 1 (postoperative day 1). Mean ± standard error. *$p < 0.05$ between baseline and EOS, LR, and HS-NS. #$p < 0.003$ between baseline and day 1, LR and HS-BS. **$p < 0.05$ between baseline and EOS, LR, and HS-NS. ##$p < 0.003$ between baseline and day 1, LR. †$p < 0.05$ between baseline and EOS, HS-NS. ††$p < 0.003$ between baseline and day 1, LR.

In summary, LR-treated patients developed hypercoagulation, which persisted for 24 hours postoperatively. HS-NS-treated patients exhibited a state of hypocoagulation at the end of surgery that was normalized by 24 hours. HS-BS treatment has a minimal effect on hemostasis as determined by thromboelastography. Additional studies are indicated to define further the clinical relevance of these findings in this and other patient populations.

AQ: 2

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CONFIDENTIAL

Executive Summary Reference #6

Coagulation effects of *in vivo* serial haemodilution with a balanced electrolyte hetastarch solution

(6 pages)

Anaesthesia, 2002, 57, pages 1–6

Coagulation effects of *in vitro* serial haemodilution with a balanced electrolyte hetastarch solution compared with a saline-based hetastarch solution and lactated Ringer's solution*

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Summary

The hydroxyethyl starches are a group of compounds that have been associated with impairment of coagulation when large volumes are administered. The thrombelastograph® is commonly used to assess point-of-care whole blood coagulation. Little is known about the dose–response relationships of haemodilution, and it is reasonable to assume that a linear association exists. This may not be the case with altered electrolyte compositions of the fluids used for haemodilution. We have therefore conducted an *in vitro* study of haemodilution of human whole blood using lactated Ringer's solution and two high molecular weight hetastarches, one in a balanced salt solution, the other in a 0.9% saline solution. The thrombelastograph®, commonly used for the assessment of the coagulation effects of synthetic colloids, was used as the coagulation assessment device. Serial haemodilution with hetastarch in a balanced salt solution demonstrated a biphasic response (of r-times and k-times, as well as alpha angles), with haemodilution in the 20–40% range causing enhanced coagulation, and higher degrees of dilution causing a decrease in overall coagulation performance. A similar picture was observed with lactated Ringer's solution, but only significantly so in alpha angles. Hetastarch in saline did not display this initial increased coagulability at mild to moderate dilutions. This biphasic response of lactated Ringer's solution and hetastarch in a balanced salt solution reflects the complex interaction of fluids and the coagulation system, and that these effects cannot be attributed to simple haemodilution. On the other hand, there was a linear decrease in maximum amplitude with haemodilution. Maximum amplitude was particularly affected by both starches, which is an expected finding in view of the known interaction between the hydroxyethyl starches and von Willebrand's factor.

Keywords *Blood*: coagulation. *Fluid balance*: intravenous fluids. *Measurement techniques.*

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* *These data have been presented in part as posters at the Annual Congress of the American Society of Anesthesiologists, San Francisco 2000, as well as at the Association of Anaesthetists' Annual Scientific Meeting, Birmingham 2000.*

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Hydroxyethyl starch (hetastarch) intravenous colloid solutions are a group of fluids that provide good volume expansion and replacement, combined with a long intravascular persistence [1]. Deleterious coagulation effects have been documented, especially when administered in large volumes of highly substituted, high molecular weight hetastarch solutions (> 20 ml.kg^{-1}) [2, 3].

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Hextend® (Abbott Laboratories, Chicago, IL, USA) is a novel formulation of 6% hydroxyethyl starch. It has an average molecular weight of 670 kDa, with a molar substitution ratio of 0.75, and is suspended in a lactate-buffered balanced electrolyte and glucose solution. Phase III clinical studies have demonstrated less derangement of thrombelastograph® variables and improved clinical indices of clotting in patients who received this fluid when compared with a similar 6% hydroxyethyl starch in saline [4]. The reason for this apparent decrease in coagulation derangement is not fully understood. As part of a series of ongoing *in vitro* and *in vivo* experiments investigating the effects of intravenous fluids on clotting, we performed serial *in vitro* dilution of human fresh whole blood with lactated Ringer's solution, 6% hydroxyethyl starch (450 kDa, 0.6 substitution ratio) in 0.9% saline (HS/saline), and 6% hydroxyethyl starch in a balanced electrolyte and glucose solution (HS/bal) in order to characterise the effect of increasing haemodilution on thrombelastograph® variables.

Of the currently used coagulation tests, the thrombelastograph® (Thrombelastograph®, Haemoscope Corp, Skokie, IL, USA) has gained wide acceptance as a reliable indicator of global dynamic clot formation, reflecting coagulation system interactions, i.e. platelet function, intrinsic and extrinsic pathways, fibrin system, as well as clot stability [5]. The developing trace one observes is a time (x-axis) vs. amplitude (y-axis) graph. The trace continues at 2 $mm.min^{-1}$, while the amplitude is measured by a torsion wire system. The wire is attached to a piston suspended in an oscillating cup (4.75°, 6 Hz) containing 360 µl of blood. No coagulation results in a straight line trace, while increasing coagulation formation displays an increasing amplitude both sides of the baseline. Its basic variables, among others, are r-time, k-time, alpha angle and maximum amplitude. The r-time reflects the time (measured in mm or min) for the first signs of coagulation (fibrin formation) to appear, in other words, the onset to clot formation. This point is marked when the amplitude of the trace reaches 2 mm, and is largely determined by circulating coagulation factors. The k-time is measured (in mm or min) from the point at which the r-time is marked to the point at which the amplitude reaches 20 mm, and represents the speed of polymerisation of fibrin once coagulation has started. Another commonly cited variable is the alpha angle, which is measured from the r-time as a tangent of the developing curve. It, too, represents polymerisation of fibrin and strengthening of the clot. The maximum amplitude reflects the total strength of the clot, and is measured as the widest amplitude of the trace obtained, i.e. the point at which the clot is the strongest (a function of mostly platelets and fibrin) [5]. Using a thromboelastograph® is cheap and easy, often giving initial results before coagulation and full blood count screens are available. This in itself is of great benefit in early correction of coagulation abnormalities in the clinical setting [6]. The thromboelastograph® is also reliable as a test for the diagnosis of a hypercoagulable state [7].

The thromboelastograph® has been used as the common denominator in many trials of the effects of haemodilution on coagulation. The reasons for this are that it is a standardised test, it provides reliable results, is easy to interpret, and provides a good reflection of the clinical coagulation state of the patient. It is an extremely useful tool for both *in vitro and in vivo* work [5]. As the thromboelastograph® measures dynamic clot formation, usually using whole blood, it is superior to common laboratory tests, e.g. prothrombin time and partial thromboplastin time, in trials investigating the effects of haemodilution on coagulation. Clinical studies have shown that when laboratory tests reflect no difference in coagulation, the thromboelastograph® is still able to reflect significant clotting differences in patients when present. Measured thromboelastograph® variables have been shown to correlate well with indices of bleeding in clinical settings [4].

Our study involves thromboelastograph® analysis of serial *in vitro* haemodilution with three intravenous fluid preparations, two of them high molecular weight hetastarch preparations (one in 0.9% saline, the other in a balanced electrolyte formulation) and lactated Ringer's solution, to assess varied electrolyte and colloid effects on the dose–response profile of haemodilution.

Methods

University of Cape Town Research Ethics Committee approval was obtained before the start of the study. Volunteer exclusions included a history of haematological disease, previous colloid intravenous infusions, or subjects receiving coagulation-altering drugs, including non-steroidal anti-inflammatory drugs. After informed consent, five healthy volunteers donated two samples per day of fresh whole blood on two separate days, i.e. four samples in total, using a two-syringe technique from a free flowing vein. The two samples in each day were separated by 90 min and were taken from different arms. The first 5 ml of each sample were discarded to minimise possible tissue factor or contact activation, and the remainder was used for mixing experiments. The fresh whole blood was immediately mixed with escalating volumes of HS/bal (Hextend®, Abbott Laboratories, Chicago, IL, USA), HS/sal (Sabax Hetastarch®, Adcock Ingram Critical Care, RSA) and

lactated Ringers solution (Intramed, RSA). The dilutional levels were 20, 30, 40, 50, 60 and 75% prepared in polypropylene tubes. The total volume for each dilution was 1 ml. The 20% dilution had 200 µl of test fluid added to 800 µl of blood, the 30% dilution had 300 µl-test fluid added to 700 µl of blood, and so on, such that the final dilution of 75% had 750 µl-test fluid added to 250 µl blood. The fluids and polypropylene tubes were prewarmed in a water bath kept at 37 °C. Each mixed sample was gently inverted eight times. Undiluted fresh whole blood control samples (total volume = 1 ml) were treated in the same way as the diluted samples before each thromboelastograph® run. The mixed samples and controls were placed in calibrated thromboelastograph® analysers (Haemoscope, Skokie, IL, USA) 4 min after venepuncture. Each thromboelastograph® was allowed to run for a minimum period of 60 min, or until the maximum amplitude was reached, as determined by the computer algorithm. The samples were rotated between the thromboelastograph® channels for different volunteers.

Analysis of variance (ANOVA) for repeated measures and two-way ANOVA, with post hoc least significant difference testing, were performed on the data obtained. Probability values ≤ 0.05 were considered to be significant. For data not normally distributed, the Kruskal–Wallis non-parametric ANOVA test was used, with the Kolmogorov–Smirnov test used post hoc to identify individual statistical differences.

Results

Significant shortening in r-time relative to the control sample was seen at 30% haemodilution with HS/bal ($p < 0.05$, Fig. 1). Dilutions of $\geq 40\%$ with HS/bal resulted in r-times that were not significantly different from control values, although the power of the test was probably inadequate to detect small changes from control at this level of dilution. Similar shortening of the k-time relative to control at 20, 30 and 40% dilution with HS/bal was seen ($p < 0.05$, Fig. 2). The maximum amplitude obtained at 75% dilution did not reach 20 mm, therefore k-times were quoted as 60 min for 75% dilutions with non-parametric statistical analysis applied to comparisons of this group with control values. Dilutions of 50% and 60% produced k-times that were not significantly different from control. The alpha angle was significantly increased relative to control at 20, 30 and 40% dilutions, with a significant decrease at 75% dilution ($p < 0.05$, Fig. 3). A progressive significant decrease from control in maximum amplitude was seen at 40–75% dilutions ($p < 0.05$, Fig. 4).

Dilution with HS/sal did not produce any decrease in r-time, but increases in r-time relative to control were seen at 50–75% dilutions ($p < 0.05$). The k-times showed a similar increase at 60% and 75% percent relative to control ($p < 0.001$), with alpha angles decreased at 50% ($p = 0.05$), 60% and 75% ($p < 0.001$), and maximum amplitudes also decreased at 40–75% dilutions relative to control samples ($p \leq 0.02$).

Interestingly, lactated Ringer's solution produced no significant differences in r-times from control values, while the k-times showed a prolongation at only 75% ($p = 0.001$). The alpha angles were consistently increased at 30–50% dilutions relative to controls ($p \leq 0.03$), and maximum amplitudes were decreased only at 60% and 75% dilutions ($p < 0.001$).

When comparisons were made at the same dilutional levels across the groups, dilution with HS/sal increased r-times at 40, 60 and 75% dilutions compared to HS/bal and lactated Ringer's solution at the same dilutions ($p < 0.05$). At 50% dilution, r-time was significantly increased with HS/sal compared to HS/bal ($p < 0.05$). The k-times showed a similar pattern: dilution with HS/sal produced longer k-times at 60 and 75% dilution than with lactated Ringer's solution at the same dilutions ($p < 0.001$), and longer k-times than HS/bal at 75%

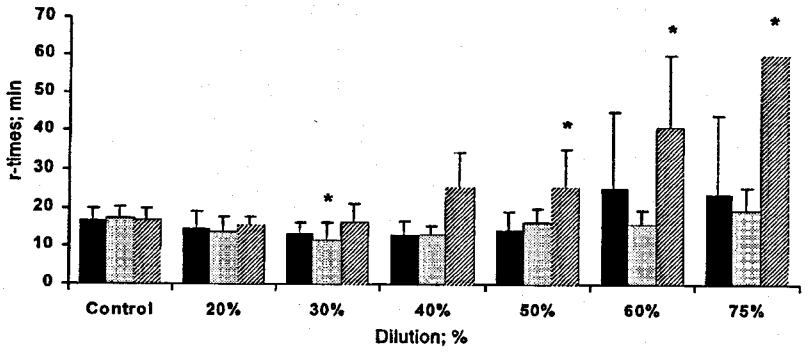

Figure 1 r-times for control (undiluted blood) and diluted samples. Error bars indicate SD. ■ dilution with lactated Ringer's solution. ▩ dilution with 6% hetastarch in a balanced electrolyte and glucose solution. ▨ dilution with 6% hetastarch in saline. * $p < 0.05$ vs. control (undiluted blood). Where no error bars are shown, no clot was formed, therefore r-time assigned as 60 min.

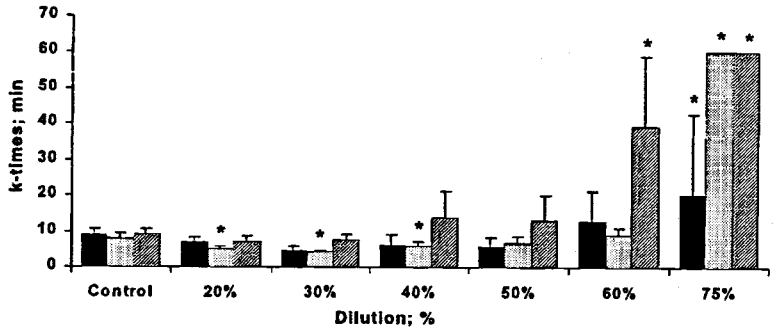

Figure 2 k-times for control (undiluted blood) and diluted samples. Error bars indicate SD. Legend as for Fig. 1. *p< 0.05 vs. control (undiluted blood). Where no error bars are shown, maximum amplitude did not reach 20 mm by 60 min, therefore k-time assigned as 60 min.

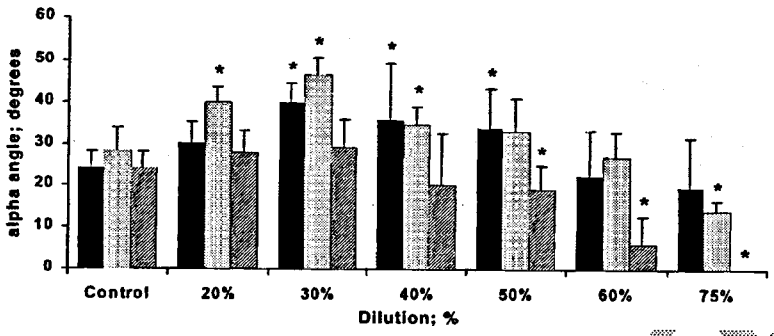

Figure 3 Alpha angles for control (undiluted blood) and diluted samples. Error bars indicate SD. Legend as for Fig. 1. *p < 0.05 vs. control (undiluted blood).

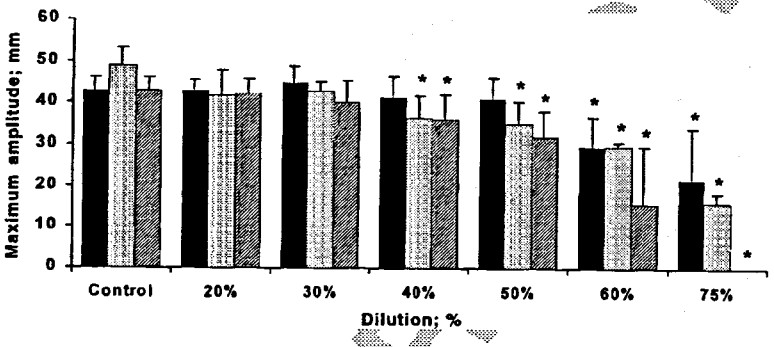

Figure 4 Maximum amplitudes for control (undiluted blood) and diluted samples. Error bars indicate SD. Legend as for Fig. 1. *p < 0.05 vs. control (undiluted blood).

dilution ($p < 0.001$). Alpha angles were consistently lower with HS/sal than with HS/bal or lactated Ringer's solution at 30–75% dilutions ($p \leq 0.01$), and lower than HS/bal only at 20% dilution ($p < 0.01$). The maximum amplitudes were decreased in HS/sal vs. lactated Ringer's solution and HS/bal at 60% and 75% dilutions ($p < 0.001$), as well as vs. lactated Ringer's solution at 50% dilution ($p < 0.02$).

Lactated Ringer's solution and HS/bal showed no significant differences between each other in r-times and maximum amplitude, but lactated Ringer's solution had shorter k-times at 75% dilution ($p < 0.001$) and smaller alpha angles at 20% dilution when compared with HS/bal ($p = 0.03$).

Discussion

Haemodilution *per se* is known to cause a disturbance in the balance between procoagulant and anticoagulant systems involved in the coagulation cascade [8]. The most common effect is one of a hypercoagulability associated with mild to moderate haemodilution. This effect occurs with all fluids, but most significantly with crystalloids [9]. This is manifested by decreased r-times and k-times, and increased alpha angles on the thrombo-elastograph®, with a varied response in maximum amplitude, depending on the fluid tested. The effect is best seen with *in vitro* haemodilution, but can also be seen *in vivo* [8].

We considered it essential to perform an observational dose–response study of HS/bal as part of ongoing work into explaining the apparent improved coagulation profile when compared with hetastarch in 0.9% saline. It is perhaps surprising that few differences were found between HS/bal and lactated Ringer's solution, as a greater hypercoagulability response would be expected with the crystalloid solution than with a hetastarch colloid [10]. Hetastarch in saline produced increasing differences as the dilutions increased, and it is possible that the electrolyte differences between HS/sal (suspended in 0.9% saline, i.e. an unbalanced electrolyte solution), and HS/bal and lactated Ringer's solution (both balanced electrolyte solutions containing calcium) were responsible. We are currently investigating the effects of electrolyte differences on the coagulation-altering effects of intravenous fluids.

The interesting significant biphasic pattern seen in r-times, k-times and alpha angles, with serial haemodilution with HS/bal (Figs 1, 2 and 3), as well as with alpha angles of lactated Ringer's solution dilution, reflects a hypercoagulability at mild to moderate haemodilution *in vitro*. This is contrary to what would commonly be expected especially of a hetastarch solution. The progressive decrease in maximum amplitude of the starches over the dilution range (Fig. 4) can be explained by the documented dose-related inhibition of von Willebrand's factor (antigen and coagulant) by HS/sal solutions [11]. Since the maximum amplitude is largely dependent on platelet function, the different behaviour of maximum amplitude with dilution in comparison to the other thromboelastograph® variables is entirely predictable. This is in contradiction to the findings of Bick, who found no significant differences in Factor VIII/von Willebrand's factor activity or structure between HS/bal dilution and saline dilution of plasma [12]. Admittedly, it was an *in vitro* study, and plasma was used rather than whole blood. Tobias *et al.* performed a serial haemodilution study, using saline, 5% albumin and a hetastarch [13]. They showed that a hypercoagulable trend developed at mild to moderate haemodilution, even in the colloid groups. They found albumin to have more hypocoagulable effects than HS/sal. Petroianu *et al.* also performed a dose–response type study, where significant decreases in r-times were found after mild to moderate haemodilution with two gelatin preparations, a dextran and certain hydroxyethyl starches [14]. A biphasic response was found in their r-times, although it was not discussed in their paper. This effect was offset by an increase in k-times and a decrease in maximum amplitudes.

Investigating the coagulation effects of a range of dilutions is necessary in explaining the varied clotting profiles that may be seen after large or small volume infusions. This must be taken into account when the results of studies are compared, as the degrees of dilution may well be different, providing conflicting results.

It is important to remember that hydroxyethyl starches, being synthetic colloids, are polydisperse fluids, i.e. they have a range of molecular sizes in a single preparation. The 'performance' and profile of these starch preparations change with time *in vivo*, as the smaller molecules (usually < 55 kDa) are rapidly filtered and excreted through the kidneys [1]. The large molecules often undergo a rapid hydrolysis, therefore leaving a colloid in the circulation with a smaller mean molecular weight and different osmotic and volume-expanding effects. In the intact subject, the coagulation system has considerable reserve capacity, both in terms of release of stored, preformed elements, and in terms of the synthesis of new coagulation proteins. Together with the metabolism of the starch particles to smaller units, this may account for the lesser effects of starches on coagulation that have been observed *in vivo* [15]. More, well-constructed, *in vivo* studies are needed to explain further the effects of intravenous fluids on coagulation.

Interactions between hydroxyethyl starches and the endothelial system are largely unexplored from a coagulation point of view. It is likely that endothelial-related coagulation plays a significant role, as the starches diminish leucocyte adherence to the endothelium, as well as modify endothelial porosity in states of capillary leak [16, 17]. However, these experiments throw no light on this aspect of coagulation, as thromboelastographic measurements exclude any consideration of platelet–endothelial interactions.

Our results therefore support the importance of performing progressive haemodilution in an attempt to determine the effects of fluids on dynamic blood clot formation. The clot onset time (r-time), as well as the clot formation rate (k-time) first decrease with mild to moderate haemodilution, then increase with gross haemodilution in the two balanced electrolyte preparations we tested. A gradual decrease in total clot strength (maximum amplitude) with progressive haemodilution was found. There was little difference between HS/bal and lactated Ringer's solution in our study, but numerous differences were found between HS/sal and the two balanced electrolyte preparations (HS/bal and lactated Ringer's solution) at the studied dilutional levels. This may be due to electrolyte composition, a subject of our research into fluids and coagulation. It is also essential to consider the dilutions used when comparing thromboelastograph® results between fluid therapy and haemodilution coagulation studies.

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Executive Summary Reference #7

Comparison of the coagulation effects of balanced electrolyte versus saline-based haemodilution using TEG *in vitro*

(2 pages)

A-199

October 16, 2001
9:00:00 AM - 11:00:00 AM
Morial Convention Center, Room C

Comparison of the Coagulation Effects of Balanced Electrolyte Versus Saline-Based Fluid Haemodilution Using TEG® *In Vitro*

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Haemodilution is known to affect coagulation in a number of ways, depending on the type of fluid, speed of infusion, as well as volume infused. Recent data suggest that electrolyte-balanced formulations may lead to less blood loss, less derangement of coagulation indices, as well as reduced metabolic acidosis[1]. This study continues a series of investigations into the coagulation effects of electrolyte balanced versus saline-based hydroxyethyl starch fluid haemodilution.
Methods: Fresh blood obtained by a two-syringe technique from free-flowing veins of healthy volunteers at 3 intervals during a single day, which was thereafter diluted by 20, 40, 60 and 80% with the following fluids:
1. 0.9% Saline (NaCl, Intramed, SA)
2. 6% Hetastarch in 0.9% Saline (HES, Sabax Hetastarch 6%® - Adcock Ingram Crit. Care, RSA)
3. 6% Hetastarch in balanced electrolyte solution (HEX, Hextend® - BioTime Inc, Berkeley, CA)
4. 6% Pentastarch in 0.9% Saline (HSter, Haes-Steril® - Fresenius Kabi, RSA)
5. 6% Pentastarch in balanced electrolyte solution (PentL, Pentalyte® - BioTime Inc, Berkeley, CA)
6. 6% Tetrastarch in 0.9% Saline (Vven, Voluven® - Fresenius Kabi, UK)
7. Human Albumin 4.5% (Alb, Western Province Blood Transfusion Service, RSA)

All diluted samples, as well as fresh, undiluted blood (Controls), were placed in TEG analysers and commenced at 6 minutes from venepuncture. Samples which had not clotted by 60 minutes were discontinued and assigned r-times of 60 minutes. Calcium levels were analysed in all samples using a Critical Care Laboratory Synthesis 25 blood gas and electrolyte machine (Instrumentation Laboratory, Lexington, MA). Statistical analysis was performed by analysis of variance and post hoc LSD testing, with $p \leq 0.05$ considered significant.
Results: There were no differences at 20% dilution. HES produced prolonged r-times compared to Controls at 40% dilution. All the fluids, except PentL, reflected prolonged r-times compared to Controls at 60% dilution. Alb (a saline-based fluid) displayed no clot formation at 60-80% dilution. At 80% dilution, none of the saline-based solutions exhibited clot formation. See table for r-time means and standard deviations of all fluids at all dilutions. Significant differences from Controls are marked [psi]. Control mean r-time was 17.0 minutes, with a standard deviation (SD) of 3.7 minutes. *Note: All unclotted samples were assigned r-times of 60 minutes, hence dilutions with means of 60 have SD = 0 minutes.*
Discussion: The electrolyte balanced formulations exhibit more favourable coagulation profiles than the saline-based formulations at moderate to severe dilutions. At 80% dilution (and at 60% dilution with Alb), no clot formation was seen in any of the salinated formulations. Alb diluted blood also had significantly lower calcium levels than all other fluids at the same dilutional levels. It is important to

consider electrolyte composition when choosing fluids for volume resuscitation.

Reference: 1. Gan TJ et al. Anesth Analg 1999; 88(5):992-8.

Anesthesiology 2001; 95:A199

	NaCl	HES	HEX	HSter	PentL	Vven	Alb
20% Dilution	13.5 (2.2)	21.4 (13.3)	13.8 (2.4)	16.3 (3.5)	15.6 (5.5)	16.7 (2.7)	15.8 (3.7)
40% Dilution	15.8 (2.0)	26.8 (10.1) [psi]	17.8 (4.2)	16.4 (7.5)	12.6 (2.9)	15.4 (2.6)	20.3 (4.7)
60% Dilution	25.9 (4.3) [psi]	48.2 (16.2) [psi]	25.7 (7.3) [psi]	35.8 (18.4) [psi]	19.1 (14.9)	29.8 (13.4) [psi]	60 (0) [psi]
80% Dilution	60 (0)[psi]	60 (0)[psi]	33.9 (17.6) [psi]	60 (0)[psi]	24.3 (17.5)	60 (0)[psi]	60 (0) [psi]

CONFIDENTIAL

Executive Summary Reference #8
An international view of hydroxyethyl starches
(11 pages)

Intensive Care Med (1999) 25: 258–268

REVIEW

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An international view of hydroxyethyl starches

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Abstract Hydroxyethyl starch (HES) is one of the most frequently used plasma substitutes. A variety of different HES solutions exist worldwide, which differ greatly in their pharmacological properties. HES is classified according to its manufactured or in vitro molecular weight (MW) into high MW (450–480 kDa), medium MW (200 kDa), and low MW (70 kDa) starch preparations. However, this is not sufficient, because as HES is metabolized in vivo, its MW changes, and it is the in vivo MW which is responsible for the therapeutic and adverse effects of each HES. The rate of metabolization depends mainly on the degree of hydroxyethyl substitution (ranging from 0.4 to 0.7), and the C2/C6 ratio of hydroxyethylation. A high degree of substitution and a high C2/C6 ratio lead to a slow metabolization of HES, resulting in a large in vivo MW.
Slowly degradable high MW HES 450/0.7 and medium MW HES 200/0.62 have a high in vivo MW and are eliminated slowly via the kidneys. As a result, these starches have a relatively long-lasting volume effect. When infusing higher volumes (> 1500 ml) are infused, large molecules accumulate in the plasma. This can result in bleeding complications due to decreased factor VIII/von Willebrand factor, platelet function defects, incorporation into fibrin clots, and an unfavorable effect on rheological parameters.
Rapidly degradable medium MW HES 200/0.5 or low MW HES 70/0.5 are quickly split in vivo into smaller, more favorable molecule sizes, resulting in faster renal elimination, shorter volume effect, and fewer adverse effects on coagulation and rheological parameters.
For historical and marketing reasons, only slowly degradable, high MW HES (480/0.7) is available in the United States. In Europe, a large variety of HES solutions are available, dominated by medium MW, easily degradable HES (200/0.5). Because of increasing international competition and the availability of newly developed starches, it is important to be aware of the pharmacological properties of HES and the advantages and disadvantages of the individual preparations.

Introduction

Although hydroxyethyl starch (HES) has been available for over two decades, great differences exist in its clinical use between Europe and the United States. In the United States, only one type of HES (480/0.7) is approved for plasma volume expansion (6% Hespan). It has the advantage of a relatively prolonged volume effect but has been associated with hemorrhagic complications. For this reason, many American physicians in

intensive care and anesthesia prefer to use albumin. From a financial point of view, HES is an attractive alternative to albumin. The exclusive use of HES could save the United States approximately US $50 million/year [1], assuming that 500 ml of albumin cost US $66 and HES US $43. Moreover, HES is significantly cheaper in Europe than in the United States, a consequence of the strong competition in the European market. In Germany, the price of 500 ml 5% albumin is also approximately $66, the price of 500 ml 6% HES 70/0.5 however is only $9 [2].

Market monopoly resulted in a high price for HES in the United States, although there the high molecular weight (MW) HES 480/0.7 (hetastarch, Hespan) has some disadvantages compared to the HES products preferred in Europe. First, the HES used in Europe are cheaper, and their use would lower costs considerably. Second, they may partly replace albumin because they affect the coagulation system only minimally – an effect shared by pentastarch (10% Pentaspan), the solution available in America for use as an erythrocyte sedimenting agent during leukapheresis. This HES solution is similar to many used in Europe, but it is not approved for plasma volume expansion.

In Europe, several HES preparations are widely used as plasma substitutes. They have many desirable pharmacologic and pharmacokinetic properties, and they are not available in all countries. For this reason, we have made an international comparison of these solutions.

Physical and chemical characteristics of HES

HES is a modified natural polymer of amylopectin with volume expansion properties. Its physical and chemical characteristics are defined by the degree of hydroxyethylation, which is the major determinant of circulating half-life, and also by its MW, which determines colloidal activity. At equal serum concentrations, the number of molecules directly dictate colloidal activity and are inversely related to the MW [3]. Solutions of native starches are unstable and rapidly hydrolyzed by plasma amylases. With minimal substitution of hydroxyethyl radicals on glucose units, solution stability is excellent, but hydrolysis is rapid and half-life very short. Kinetics of elimination is improved by higher substitution, which is quantified by the molar substitution ratio or by the degree of substitution [3]. The degree of substitution is determined by measuring the number of substituted glucose molecules and dividing this number by the total number of glucose molecules present. The molar substitution ratio is computed by counting the total number of hydroxyethyl groups present and dividing the number by the quantity of glucose molecules. Although these numbers are not the same, they are often incorrectly used interchangeably in the literature. Different molar substitution ratios, from 0.4 to 0.7, have been used. For example, HES 480/0.7 has an in vitro MW of 480000 Da and a molar substitution ratio of 0.7.

Table 1 Characteristics of the different types of HES[a] (*MW* molecular weight)

Concentration	
High	10%
Low	6%
Initial MW	
High	450–480 kDa
Medium	130–200 kDa
Low	40–70 kDa
Degree of substitution	
High	0.6–0.7
Low	0.4–0.5
C2/C6 ratio	
High	> 8
Low	< 8

[a] Two types of concentrations are available, the initial MW can be divided into three groups, and the degree of substitution and the C2/C6 ratio can be high or low

The hydroxyethylation can occur at carbon positions 2, 3 or 6 of the glucose molecule, depending on manufacturing. Also, individual glucose molecules can have from zero to three hydroxyethyl groups. Production processes for HES vary in the United States, Europe, and Japan, as do the raw materials, which can be corn or potato starches. Therefore, the resulting product can vary greatly in the substitution pattern. The substitution type is identified by the C2/C6 hydroxyethylation ratio. The higher the ratio – that is, the higher the number of glucose molecules hydroxyethylated at the C2 atom versus the C6 – the slower the starch metabolizes. Thus, the hydroxyethylation pattern greatly influences in vivo characteristics of HES solutions – even if they have similar MWs [4].

The molecular weight of the solutions is the second important factor determining colloidal effect and pharmacokinetics. HES molecules show great polydispersity, and molecule sizes in any one solution follow a bell-shaped distribution, ranging from a few thousand to a few million daltons. The molecular weight can be regarded as the average molecular weight, which is a simple arithmetic mean, or as weight averaged molecular weight (MW). The MW is most commonly used in clinical medicine. Table 1 gives an overview of HES solutions in common use [5–10].

Pharmacokinetics of HES

Shortly after HES infusion, the MW distribution of the circulating molecules becomes narrower and the average MW value smaller than that of the infused solution

[11,12]. This indicates that small molecules with an MW smaller than 50000 Da are rapidly cleared by renal excretion and that larger molecules are hydrolyzed by amylase into smaller molecules. The pattern of change in MW distribution of most HES preparations is similar, e.g., the MW decreases from 200000 Da of the infused solution to 72000 Da in plasma during the first few hours following infusion. This limited hydrolysis by the amylases increases the number of molecules and reinforces the osmotic effect, since the latter is proportional to the number of circulating molecules. The molar substitution ratio of the circulating HES molecules also increases slightly from that of the infused solution, as the more highly substituted molecules resist hydrolysis.

The role of intravascular cleavage of HES is debated by some authors. For a medium MW HES (HES 200/0.62) it has been demonstrated that intravascular hydrolysis was minimal [13]. In this theory, the reticuloendothelial system plays a major role in the elimination of HES molecules with a high degree of substitution and a high C2/C6 ratio. At the present time, the precise mechanism of complete elimination of HES is still the subject of discussion.

Pharmacodynamics of HES in anesthesia and intensive care

Data concerning the extent and duration of plasma volume expansion are difficult to compare. The subjects studied vary from normal volunteers to patients with normal or low plasma volume and, at times, with low plasma protein concentrations. Changes in capillary permeability due to septic shock and hemorrhagic shock and cardiopulmonary bypass can influence the disposition of colloids and water. The rate of administration of plasma substitutes also affects the volume of expansion. Finally, the method of quantifying expansion varies – results obtained with radiolabeled albumin may differ from those obtained using labeled red blood cells.

One of the first clinical studies using HES 480/0.7 in humans was performed in mild hypovolemia [14]. Most available data have since demonstrated that 500 ml of 6% HES 480/0.7 administered over 60 min expands plasma volume by 300 ml in normovolemia and by 720 ml in hypovolemia [15–27]. Doubling the total dose from 500 to 1000 ml resulted in greater expansion but not one that was twice as large. The duration of action of 500 ml of 6% HES 480/0.7 appears to average 24 h.

The effects of fluid resuscitation using 6% hetastarch, 5% albumin, or 0.9% saline solutions have been compared in patients with hypovolemic shock [28]. One liter of hetastarch produced a 36% increase in colloid osmotic pressure (COP) compared to an 11% increase after 1 liter of albumin. One liter of saline resulted in a 12% decrease in COP. Saline resuscitation required significantly larger amounts of fluid (6371 ml) than albumin (3134 ml) and hetastarch (4466 ml). These results were compared in another study using the same protocol design, demonstrating that resuscitation with saline resulted in a higher incidence of pulmonary edema (87%) than resuscitation with albumin (22%) or hetastarch (22%) [5]. Moreover, 10% hetastarch was more efficient than Ringer's lactate solution in improving hemodynamics and oxygen transport variables in critically ill patients [29].

Clinical use of hetastarch as a prime for cardiopulmonary bypass (CPB) has been evaluated in several studies [21–23, 30]. When compared to albumin, no difference in chest tube drainage, blood use or coagulation times was detected [30]. In comparing hetastarch to albumin and lactated Ringer's solution as a priming fluid [21], the Ringer's group had a significantly longer COP than the others, and the hetastarch group had a substantially higher blood viscosity. No clinically relevant difference in hemostasis, chest tube drainage or blood transfusions emerged. Postoperatively, pulmonary shunt fraction and the increase in body weight were greater in patients who received Ringer's solution. No difference between 25% albumin and 6% hetastarch on extravascular lung water was found during and after CPB [23]. Only one study brought conflicting results, showing that a hetastarch group needed higher volume replacement and blood use than an albumin group [22]. Higher chest tube drainage was also observed, suggesting impaired blood coagulation.

Hetastarch has been compared to albumin for colloid infusion following CPB in patients undergoing myocardial revascularization [6]. Cardiac index, atrial pressure, heart rate and systolic blood pressure were similar, as well as weight change during the first 7 postoperative days or changes in COP. However, the patients receiving HES had higher prothrombin time and partial thromboplastin time and showed a trend toward higher cumulative postoperative bleeding. Clinical comparison of albumin and hetastarch in postoperative cardiac surgery patients has confirmed that hetastarch is as efficient as albumin [7, 8].

All these clinical data suggest that plasma volume expansion induced by 6% hetastarch and the same volume of 5% albumin are similar. However, effects on hemostasis and prolonged accumulation of hetastarch, in some respects, pose serious limitations to the clinical use of this type of HES.

Many studies have documented the clinical efficacy of medium MW HES [15, 16, 31]. In a randomized clinical trial, the clinical efficacy and safety of pentastarch were compared with 5% serum albumin for plasma volume expansion after cardiac surgery [10]. During the first 24 h, colloidal solution was infused to maintain cardiac index and arterial pressure within normal values. Hemodynamic responses were similar in both groups.

although a greater increase in cardiac index was observed during infusion of the first 500 ml of pentastarch. There were no significant differences in any of the measured respiratory parameters and, especially, in venous admixture. Hemodilution with pentastarch reduced serum protein levels, although COP was similar in the two groups. Perioperative fluid balance, weight change, chest tube drainage, and blood transfusion of products were also similar.

The effects of pentastarch on cardiorespiratory function have been compared to 5% albumin in patients with severe sepsis and shock [32]. 250 ml of test colloid was administered every 15 min until the pulmonary artery occlusion pressure was 15 mmHg or a maximum dose of 2000 ml was infused. The volume of colloid required to achieve this goal was comparable between the groups.

Several studies demonstrated that a medium MW HES 200/0.62 induces a larger volume expansion than the infused volume [13]. In a study performed during recovery after general anesthesia, 6% HES 200/0.62 induced an initial plasma volume expansion greater than the infused volume and had a prolonged effect. Only limited MW distribution changes were observed, suggesting that intravascular hydrolysis of large molecules probably does not reinforce the colloid osmotic effect. These data could suggest that a low HES elimination rate or extravascular mobilization is the main mechanism explaining prolonged plasma volume expansion with HES 200/0.62.

A comparison has also been made between 6% HES 200/0.62 and 4% albumin in a 24-h randomized study using intentional hemodilution, a well-standardized method used to study the effects of plasma substitutes over a long period [25]. End points were blood volume measurements as well as hemodynamic and hormonal effects. Patients scheduled for abdominal aortic surgery were included in the study. In both groups, cardiac index increased after the exchange, and persisted until the 24th h. Plasma renin activity decreased in both groups after hemodilution until the 24th h. These data suggest that 6% HES 200/0.62 as well as 4% albumin were capable of maintaining normovolemia during a 24 h period after intentional hemodilution.

The hypovolemic model was also used in test subjects to determine the volume effect of 500 ml 10% dextran 40, 10% HES 200/0.5, 6% HES 200/0.5, and 5.5% oxypolygelatin [15]. Dextran 40 and 10% HES 200/0.5 exhibited a stable volume effect over a period of 8 h, the former having a more pronounced effect, and there was a consistent increase in the blood volume equivalent to more than double the infused volume. The longer rise in colloid osmotic pressure after HES infusion corresponded to the higher colloid osmotic pressure in the infusion solution; 6% HES 200/0.5 also led to stable volume replacement. Two hours after infusion, 52% of the infused HES 200/0.5 remained in the intravascular space, 35% after 4 h, and 21% after 8 h. By contrast, the volume expansion effect of oxypolygelatin is such that only 10% of the infused volume is present after 2 h, 5% after 4 h, and 2% after 8 h.

Table 2 Effects of a 10-day infusion therapy with HES in patients with cerebral perfusion disorders [34–37]

	Type of HES			
	200/0.62	200/0.5/13	200/0.5/6	70/0.5
Total amount infused in grams	500	750	750	450
In vivo MW in kDa on day 10	120.6	95.0	84.1	57.5
Comparative degradation rate	Slow	Slow	Fast	Fast
Serum concentration after 10 days in g/l	25.3	12.0	5.8	2.6
Volume effect gauged as decrease in hematocrit (%)	19.0	22.4	22.3	16.0

Studies in which blood was aspirated in a stepwise manner and isovolemically replaced with 6% dextran 60 or with HES 6% solution (HES 450/0.7 and HES 70/0.5) [33] revealed adequate volume expansion only with dextran 60 and high MW HES 450/0.7, but not with low MW HES 70/0.5.

Overall, many studies comparing albumin and HES have shown the efficacy of HES as a volume expander. Depending on the HES used, the plasma expansion induced by HES can be comparable to albumin. Stable plasma volume expansion can be obtained with both high MW HES and medium MW HES, while low MW HES have a short effect. Medium MW HES result in a less pronounced accumulation of molecules than high MW HES. The accumulation, however, also depends on the degree of hydroxyethylation and the C2/C6 ratio.

Pharmacodynamics of repeated administrations of HES

To distinguish between five different HES types, the pharmacodynamics of a 10-day volume therapy were studied in 50 patients with cerebral perfusion disorders [34–37]. Table 2 summarizes the findings. Compared to all HES solutions studied, the highly substituted HES 200/0.62 was the slowest to degrade. The in vivo MW of 120 kDa was the highest studied: this made macromolecule elimination difficult, caused an accumulation of molecules, and led to an increase of the serum concentration to 25.3 g/l. The serum concentration for modestly degradable HES 200/0.5 measured at day 10 was 12.0 g/l (i.e., double that of rapidly degradable HES 200/0.5). HES 70/0.5 undergoes little change from its ini-

tial in vivo MW of 60 kDa, and there is neither an accumulation of slowly degradable molecules nor an increase in serum concentration. The serum concentration determined after 10 days of therapy was only one-tenth of that for HES 200/0.62.

The volume expansion effect of HES can be estimated via the changes in the hematocrit. HES 200/0.62 results in a decrease of 19.0%. HES 200/0.5 with a C2/C6 ratio of 13 and HES 200/0.5 with a C2/C6 ratio of 6 reduces the hematocrit similarly (–22.4 and –22.3% respectively). HES 70/0.5 causes a decrease in hematocrit of 16.0%. HES 200/0.62, depending on the dose, shows the most continuous volume effect. The volume effect of HES 70/0.5 is quite remarkable despite a relatively low dose. The volume effect depends less on the molecule size than on the colloidal-osmotic action of the molecules. Comparable studies on long-term volume substitution with HES 480/0.7, which is mainly used in the United States, do not yet exist. This starch has a substitution degree of 0.7 and may degrade even more slowly than HES 200/0.62. At a high initial MW, the in vivo MW may be 200 kDa. It has the longest half-life of all HES, but the remaining molecules are fewer and relatively large, so that it is unclear how long-lasting the volume effect would be.

Considering that the objective of infusing these solutions is to achieve a volume effect with as few side effects as possible, either easily degradable HES 70/0.5 or HES 200/0.5/6 seems to be a reasonable choice. Both result in a relatively low serum concentration of smaller molecules. As discussed below, it is possible that larger molecules are responsible for the adverse effects of HES, such as itching and rheologic and hemorrhagic problems. Therefore, HES with smaller in vivo MWs and lower serum concentrations are desirable.

Adverse effects of HES

Effects not related to coagulation

The rate of anaphylactoid reactions to HES is approximately 0.006% of infusions, which is considerably lower than the incidence after the administration of dextran [33]. A recent study of 19593 patients determined the frequency and severity of allergic reactions according to the type of colloids available in France [27]. The frequency differed significantly according to the colloid considered: 0.345% for gelatins, 0.273% for dextrans, 0.099% for albumin, and 0.058% for HES. These reactions (grades III and IV) were serious in 20% of cases. Because the existence of preformed antibodies against HES is extremely rare, it has been postulated that HES directly activates complement to mediate anaphylactoid reactions that are responsible for allergic reactions to HES. Recently, however, a patient with specific antibodies to HES has been reported. Currently, the precise reason why allergic reactions to HES occur is not known.

Therapy-resistant pruritus is a frequent adverse effect that occurs only after chronic administration of HES. The dose-dependence and the long latency period prior to the onset of pruritus suggest that it is the result of extravascular starch deposits [38–40].

A regularly observed increase in serum amylase after HES infusion of up to five times the initial value has no pathological relevance because it does not affect the pancreas or lipase activity [15, 37]. Amylase attaches to the starch molecules and therefore escapes renal excretion, resulting in macroamylasemia. For several days after HES therapy, the serum amylase cannot be used as a diagnostic parameter for pancreatitis.

Effects on transplanted kidneys

Adverse effects of HES on transplanted kidneys remain a subject of controversy. Osmotic-nephrosis-like lesions have been reported in transplanted kidneys subsequently biopsied at Hopital Necker in Paris [41]. In a historical study, 80% of kidneys transplanted at a center during 1992, when routine administration of HES 200/0.62 to the donor was implemented, had osmotic nephrosis-like lesions in biopsy specimens taken 6 weeks after transplantation. Only 14% of the kidneys transplanted during 1990, prior to the implementation of HES administration, displayed such lesions. In a prospective study of 69 brain-dead patients randomized into two groups [42], donors received up to 33 ml/kg HES for colloid plasma volume expansion, and afterwards received modified fluid gelatin. In a gelatin-only group, donors received only modified fluid gelatin as colloidal plasma volume expander. Multiple organs were procured in 29 cases, which included the kidneys in 27 cases (HES group, $n = 15$; gelatin, $n = 12$). During the first 8 days posttransplantation, 9 of 27 (33%) patients required extrarenal hemodialysis or hemodiafiltration in the HES group, compared with 1 of 20 (5%) in the gelatin group ($p = 0.029$). Serum creatinine concentrations were significantly lower in the gelatin group than in the HES group. By contrast, analysis of 24 renal transplant biopsy specimens taken 15 min after kidney reperfusion [43] revealed that osmotic nephrosis-like lesions were less frequent (25%) than previously reported [42]. The use of HES in donors did not influence the frequency of these lesions. None of these studies identified HES in the vacuoles seen on renal biopsy, indicating no direct relationship with HES administration. It was concluded that the hemodynamic status of the donor is still the main determinant of the occurrence of these lesions [43]. However, all these studies are limited to a few subjects, and a large-scale study is needed to draw firm con-

clusions. Until then, it is advisable to use HES 200/0.62 as a plasma volume expander but with caution in brain-dead donors and in kidney transplant recipients.

Effects on coagulation

In the United States, bleeding complications after infusions of HES 480/0.7 (hetastarch) have been reported repeatedly – usually after fairly high doses [44–52]. Significant bleeding complications were reported during HES 480/0.7 therapy administered for several days in patients with subarachnoid hemorrhage, as treatment for vascular spasm [53]. By contrast, other investigators found that HES 480/0.7, when given in doses lower than 1.5 l, does not increase bleeding beyond the extent expected of other colloidal solutions [7, 21, 54, 55].

As reviewed previously, HES 480/0.7 produced minor effects on clotting when infused in moderate amounts (doses not exceeding 20 ml/kg, 800 ml/m^2, or 1500 ml total volume over 24 h) [54]. Blood platelet counts were unchanged or decreased transiently and remained above levels required for normal hemostasis (> 100000/ml). Bleeding times and platelet aggregation to a variety of agents were generally normal. Plasma clotting times and specific clotting proteins either remained normal or exhibited only slight alterations. Even when these parameters were abnormal, specific clotting proteins were present in amounts sufficient to ensure effective hemostasis. Thus, HES infused in moderate doses produced effects on clotting that were transient and trivial.

After massive doses of HES 480/0.7 (> 25% of patient total blood volume), laboratory abnormalities were detected in all aspects of hemostasis, and overt hemorrhage was frequently observed. Thrombocytopenia occurred, platelets appeared swollen, and platelet adhesion was decreased. Concentrations of several clotting proteins decreased, accounting for prolonged clotting times. Fibrin clots formed slowly and appeared to lack a tight meshwork, were friable, and exhibited decreased tensile strength.

To investigate the effects of colloidal solutions in trauma patients, an open, randomized, parallel trial was conducted, comparing the effects of 6% HES 480/0.7, 5% albumin, and 0.9% NaCl [54, 55]. Each of the three study groups consisted of ten patients. An immediate decrease in fibrinogen concentration occurred after a 1-l infusion of either HES or albumin, but not after NaCl. In none of the study groups did the mean fibrinogen values fall below 170 mg/dl (i.e., 100 mg/dl adequate concentration for normal hemostasis). When the results were adjusted for the diluting effects of plasma volume expansion, all significant decreases in fibrinogen levels disappeared. Thus, HES and albumin exerted no effects that were independent of hemodilution. Prothrombin time remained normal in all three groups. Partial thromboplastin time (PTT) in the group receiving hetastarch was prolonged. One clotting protein important for maintaining a normal PTT is factor VIII. An immediate decrease in factor VIII of approximately 50% occurred only in the group receiving HES. The effects of HES on factor VIII exceeded those attributed only to hemodilution and, presumably, were due to additional mechanisms. After HES infusion, the mean bleeding time was prolonged from a baseline value of 7.2 to 9.4 min 4 h postinfusion. Similar values before and after albumin infusion were 6.8 and 9.5 min, respectively. Although postinfusion bleeding times were long ($p < 0.05$), they were not significantly different from values with saline and were within the normal range (2.5 to 9.5 min). Mean values for platelet count, platelet adhesion, and circulating platelet aggregates remained within the normal range, and there was no detectable difference among groups. Thrombin-, reptilase-, and urokinase-activated clot lysis times were significantly shorter after HES infusion ($p < 0.05$). However, fibrin monomer and fibrin-fibrinogen degradation products were not increased. Thus, the major effects of HES are dilution of plasma clotting proteins, an additional decrease of factor VIII, and accelerated fibrin clot formation in the final stage of clotting.

In Europe, bleeding complications have been described after hetastarch administration, after infusion of HES 270, and after infusion of slowly degradable HES 200/0.62 [57–59]. In Germany, where rapidly degradable HES 200/0.5 and HES 70/0.5 are preferred as colloidal plasma substitutes, clinically relevant bleeding complications have not yet been reported. Although reported data seem to be contradictory, and the true risk of bleeding complications for patients treated with HES seems difficult to predict, clinical bleeding is greatly influenced by the quantity of HES infused, the preparation selected, whether single or multiple infusions are given, the nature of other fluids infused (e.g., plasma), and the medical condition of the patient (e.g., underlying coagulation abnormalities or thrombocytopenia).

Pentastarch 264/0.45 is similar to HES 200/0.5 preparations available in Europe and exerts fewer effects on coagulation than HES 480/0.7 [54, 56]. Clotting studies were performed and the results compared using doses of pentastarch and hetastarch that produced similar postinfusion plasma concentrations of HES. Although fibrinogen concentrations were decreased after infusions of both preparations, the decrease after pentastarch infusion was significantly greater than after hetastarch infusion, suggesting greater hemodilution and plasma volume expansion by pentastarch. PTT was prolonged was prolonged to a similar extend by both forms of HES, and factor VIII was decreased, but the predominant effect of pentastarch seemed to be mediated by hemodilution. By contrast, the effects of hetastarch on

Table 3 Influence of HES on coagulation during a 10-day hemodilution therapy (*MW* molecular weight, *PTT* partial thromboplastin time, *F.VIII* factor VIII, *vWF/AG* von Willebrand antigen)

Type of HES	In vitro MW (kDa)	Degree of substitution	C2/C6 ratio	In vivo MW	PTT (%)	F.VIII (%)	vWF/AG (%)
Slowly degradable medium MW HES	200	0.62	10	120.6	+42.8	−70.4	−83.6
Slowly degradable medium MW HES	200	0.5	13	95.0	+16.6	−24.6	−17.6
Rapidly degradable medium MW HES	200	0.5	6	84.1	+7.9	−7.9	−6.1
Rapidly degradable low MW HES	70	0.5	4	57.5	+4.0	+8.2	−1.9

factor VIII were more profound, and levels were decreased below those that could be ascribed to hemodilution. Thrombin times were shortened by both preparations, but the effect of hetastarch was significantly greater than that of pentastarch. Pentastarch exerted no effect on the urokinase-activated clot lysis time, whereas hetastarch significantly shortened it. Hetastarch, but not pentastarch, significantly prolonged the bleeding time. Thus, pentastarch 264/0.45 in modest doses had no apparent effects on coagulation beyond those produced by hemodilution.

Systematic studies on the influence of a 10-day volume therapy of the most commonly used European HES products showed differences among the numerous HES products [34–37]. Patients received up to 7500 ml of HES (450–750 g total dose) over 10 days. The infusion of a large volume of HES over 10 days showed effects on coagulation that could not be observed after a one-time administration or an administration of moderate doses. There were remarkable differences in the influence on the activated PTT (aPTT). Table 3 summarizes the findings for aPTT, factor VIII, and von Willebrand factor antigen.

The prolonged aPTT that was observed after HES 200/0.62 or slowly degradable 200/0.5 was found to result from an impaired factor VIII/von Willebrand (vWF) complex [60]. The decrease in the VIII/vWF complex is the more pronounced the higher the HES dose, the initial MW, the C2/C6 hydroxyethyl ratio, and, in particular, the degree of hydroxyethyl substitution. An in vivo complexing and clearance of VIII/vWF by HES has been postulated. Since patients with monoclonal gammopathy can acquire von Willebrand's disease, an accelerated elimination of the VIII/vWF after complexing with HES seems possible [64]. This idea is supported by the demonstration of an F.VIII-IgG-paraprotein complex [65]. The greater the number of macromolecules which are difficult to eliminate, the more severe the coagulation disorder [34–37]. Thus, bleeding complications can be avoided by choosing HES with a relatively low in vivo MW and a low degree of hydroxyethylation. The coagulation impairment induced by high in vivo MW HES seems to correspond to von Willebrand syndrome type I [54, 60]. This suggests possible therapy, since the von Willebrand syndrome type I is treated with the vasopressin derivative desmopressin [61, 62]. However, efficacy has not been shown. With in vitro studies, where HES is added to human serum, it has been shown that VIII/vWF complex did not decrease beyond levels lowered by dilution [55, 63].

Additional findings of the HES 10-day volume therapy study also depended strongly on the preparation of HES administered [34–37]. A reduction of the thromboplastin time (Quick) of 20% was most pronounced after HES 200/0.62. Although factors II, V, VII, IX and X were not influenced beyond the dilution effect, factors XI and XII were reduced further to about half of their initial value, after administration of the higher substituted HES 200/0.62 [37]. Decreases in factors XI and XII were not seen with rapidly degradable HES 200/0.5. This suggests that the impairment of the intrinsic system may not be restricted to factor VIII – a hypothesis that requires further study.

The initial dilution-dependent decrease in platelet count was followed by an increase in the platelet count, which may be the result of a reactive release of platelets [66–68]. A minor, but significant decrease in mean platelet volume occurred after medium as well as after low MW HES. Studying the MW distribution shows that the decline in platelet volume is more marked the higher the in vivo MW of the applied starch. The importance of a decreasing platelet volume is not clear [69, 70]. Several studies suggest that platelet volume, platelet function and bleeding time are related [69, 71–73]. As a result, it can be hypothesized that platelet volume and platelet function both decline during volume therapy with repeated and prolonged doses of HES. However, the significant reduction in platelet volume appeared to influence platelet function only slightly, because platelet aggregation was only moderately inhibited.

Overall, the combined data of the presented studies shows that HES with a high initial molecular weight or HES with a high in vivo molecular weight has unfavorable effects on coagulation. These side effects can be avoided through the use of medium or lower molecular weight HES that is easier to degrade.

Table 4 Effects of HES hemorheology (*MW* molecular weight)

Type of HES	In vitro MW (kDa)	Degree of substitution	C2/C6 ratio	In vivo MW	Plasma viscosity (%)	*p* value
Slowly degradable medium MW HES	200	0.62	10	120.6	+ 18.5	< 0.01
Slowly degradable medium MW HES	200	0.5	13	95.0	+ 10.1	< 0.01
Rapidly degradable medium MW HES	200	0.5	6	84.1	+ 3.1	NS
Rapidly degradable low MW HES	70	0.5	4	57.5	− 1.5	NS

Table 5 Summary of the advantages and disadvantages of the different types of HES

Slowly degradable, high MW HES 480/0.7	Disadvantage Coagulation disorders Deterioration of rheological parameters Negative effect on the reticuloendothelial system? Advantage Long-lasting volume effect
Slowly degradable, medium MW HES 200/0.62	Disadvantage Coagulation disorders Deterioration of rheological parameters Negative effect on the RES? Advantage Long-lasting volume effect
Rapidly degradable, medium MW HES 200/0.5	Advantage Hardly any coagulation disorders Improvement of rheological parameters Mean duration of volume effect
Low MW HES 70/0.5	Disadvantage Short-lasting volume effect Advantage Only dilution effect on coagulation Fast improvement of rheological parameters Good control

Effects of HES on hemorheology

Plasma viscosity is an important factor contributing to the microcirculatory disturbances that characterize shock. Plasma viscosity is determined in large part by the number and physical properties of macromolecules in the plasma, such as fibrinogen. Table 4 summarizes the data of a study comparing the effects of different HES on hemorheology [37]. When administering highly substituted 10% HES 200/0.62, an 18.5% increase in plasma viscosity was observed. The increase depended on the infusion rate of HES and developed in parallel with the HES serum concentration. On the other hand, HES 200/0.5 with a low C2/C6 ratio and low MW HES decreased plasma viscosity – providing enough fluid was administered at the same time to compensate for dehydration as determined by the hematocrit. During a hemodilution therapy with HES 450/0.7, a pronounced increase in plasma viscosity was reported [74]. Because of its high initial MW and the high degree of substitution, this starch solution has a high intravascular MW, which explains the increase in plasma viscosity.

The different HES solutions have variable effects on other rheological parameters, including erythrocyte aggregation or sedimentation rate. Erythrocyte aggregation is the result of a reversible bridge formation, consisting of large HES molecules between the erythrocytes, which can not get closer than 30 nm to each other, due to Coulomb forces. Erythrocytes attach to each other only if larger molecules, such as fibrinogen, form bridge-like structures between the erythrocyte membranes [75]. Smaller molecules can push away the larger molecules that facilitate erythrocyte aggregation and therefore lead to a decrease in aggregation [76, 77].

One explanation of the differing behavior is the distribution of the in vivo MW. During a short infusion with dextran, the smaller molecules dominate with their tendency to lower erythrocyte aggregation. A repeated administration, however, leads to the accumulation of macromolecules that are difficult to eliminate and cause an increase in erythrocyte aggregation [78, 79]. HES molecules, on the other hand, are metabolized in vivo and the resulting smaller molecules lower erythrocyte aggregation. Only a "loading dose" of 10% HES 200/0.62 leads to an initial increase due to the massive appearance of large molecules [77]. During the course of further therapy, the large molecules are enzymatically degraded and smaller molecules dominate, leading to a decrease in erythrocyte aggregation. Slowly degradable HES 200/0.62, high MW HES most likely affects the aggregation considerably because of its high in vivo MW. When infusing HES 70/0.5, the "loading dose" provides a large number of small molecules, leading to a rapid 27% drop in erythrocyte aggregation.

Because of the complexity of rheological and hemostatic processes in vivo, it is difficult to assess the effects of HES in vitro [82]. Data collected in vivo suggests that, from a rheological perspective, highly substituted medium or high MW HES are less desirable, because they increase plasma viscosity. Medium or low MW starches with a low degree of substitution and a resulting low in vivo MW have better rheological properties.

Conclusion

A large variety of HES preparations exist worldwide, differing in concentration, initial molecular weight, degree of substitution, and C2/C6 ratio. In Europe, rapidly degradable medium MW HES 200/0.5 preparations are preferred. For historical and marketing reasons, slowly degradable high MW HES 480/0.7 preparations are more popular in the United States. HES solutions that are difficult to metabolize have the advantage of a long-lasting volume effect. However, repeated infusions or the infusion of larger volumes (> 1500 ml) leads to the accumulation of macromolecules that are difficult to eliminate by the body. This, in turn results in an impairment of the coagulation system through a decrease in factor VIII/vWF and to a worsening of rheological parameters. Easily degradable medium MW HES 200/0.5 or low MW HES 70/0.5 do not have these disadvantages, but the duration of their volume effect is shorter due to their faster elimination. This can be compensated for through repeated infusion.

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