L'ipovolemia da emorragia intra- e post-operatoria: quando i cristalloidi non bastano?

Intra- and post-operative bleeding-associated hypovolemia: when crystalloids are not enough?

Andrea De Gasperi

Special Conference
Il Patient Blood Management: non solo una questione di ferro e anemia
Roma, 15 ottobre 2015

Società Italiana
di Medicina Trasfusionale
e Immunoematologia

SIMTI

Special Conference on

Patient Blood Management: not only a question of iron and anaemia

SECOND SESSION
PBM: beyond the first pillar

Chairmen: Pierluigi Berti - Giuliano Grazzini

14.00 Transfusion medicine and anaemia clinics: does all end here? *Stefania Vaglio*

14.30 Restrictive transfusion strategy: guidelines and real life - *Gianni Biancofiore*

15.00 Intra- and post-operative bleeding-associated hypovolemia: when crystalloids are not enough? *Andrea De Gasperi*

15.30 PBM and the management of the patient on oral anticoagulant - *Domenico Prisco*

16.00 Discussion

16.30 End of the conference

Patient blood management: a fresh look at a fresh approach to blood transfusion

G. M. LIUMBRUNO [1], S. VAGLIO [2], G. GRAZZINI [3], D. R. SPAHN [4], G. BIANCOFIORE [5]

From this point of view, the reduction of allogeneic blood usage is not an end in itself but a tool to achieve better patient clinical outcome. This article focuses on the three-pillar matrix of patient blood management where the understanding of basic physiology and pathophysiology is at the core of evidence-based approaches to optimizing erythropoiesis, minimising bleeding and tolerating anemia. Anesthesiologists and critical care physicians clearly have a key role in patient blood management programmes are and should incorporate its principles into clinical practice-based initiatives that improve patient safety and clinical outcomes. *(Minerva Anestesiol 2015;81:1127-37)*

Anesthesiology 2012; 116:1367–76

Patient Blood Management

Lawrence Tim Goodnough, M.D.,* Aryeh Shander, M.D.†

Patient Blood Management

	Optimize erythropoiesis	Minimize blood loss	Manage anemia
PREOPERATIVE	• Identify, evaluate, and treat underlying anemia • Preoperative autologous blood donation • Consider erythropoiesis stimulating agents (ESA) if nutritional anemias ruled out/treated • Refer for further evaluation if necessary	• Identify and manage bleeding risk (past/family history) • Review medications (antiplatelet, anticoagulation therapy) • Minimize iatrogenic blood loss • Procedure planning and rehearsal	• Compare estimated blood loss with patient-specific tolerable blood loss • Assess/optimize patient's physiologic reserve (e.g., pulmonary and cardiac function) • Formulate patient-specific management plan using appropriate blood conservation modalities to manage anemia
INTRAOPERATIVE	• Time surgery with optimization of erythrocyte mass (note: unmanaged anemia is a contraindication for elective surgery)	• Meticulous hemostasis and surgical techniques • Blood-sparing surgical techniques • Anesthetic blood conserving strategies • Acute normovolemic hemodilution • Cell salvage/reinfusion • Pharmacologic/hemostatic agents	• Optimize cardiac output • Optimize ventilation and oxygenation • Evidence-based transfusion strategies
POSTOPERATIVE	• Manage nutritional/correctable anemia (e.g., avoid folate deficiency, iron-restricted erythropoiesis) • ESA therapy if appropriate • Be aware of drug interactions that can cause anemia (e.g., ACE inhibitor)	• Monitor and manage bleeding • Maintain normothermia (unless hypothermia indicated) • Autologous blood salvage • Minimize iatrogenic blood loss • Hemostasis/anticoagulation management • Be aware of adverse effects of medications (e.g., acquired vitamin K deficiency)	• Maximize oxygen delivery • Minimize oxygen consumption • Avoid/treat infections promptly • Evidence-based transfusion strategies

Fig. 4. Patient blood management. These principles applied in the perisurgical period enable treating physicians to have the time and tools to provide patient-centered evidenced-based patient blood management to minimize allogeneic blood transfusions. ACE = angiotensin-converting enzyme.

RACCOMANDAZIONI PER L' IMPLEMENTAZIONE DEL PROGRAMMA DI PATIENT BLOOD MANAGEMENT

APPLICAZIONE IN CHIRURGIA ORTOPEDICA MAGGIORE ELETTIVA DELL' ADULTO

Liquidi di infusione

La correzione dell'ipovolemia da emorragia mediante infusione di cristalloidi e/o collodi ha un ruolo prioritario nella gestione dei pazienti con sanguinamento acuto o sub-acuto ed è la prima strategia alternativa alla trasfusione allogenica, poiché l'ipovolemia acuta è meno tollerata rispetto all'anemia[27]. Pertanto, un adeguato reintegro del volume circolatorio e, di conseguenza, della gittata cardiaca, permette il mantenimento del trasporto di ossigeno ai tessuti. Tuttavia, nel paziente con emorragia critica, è ancora oggetto di dibattito quale sia la migliore strategia di reintegro della volemia con fluidi [223].

a cura di

Stefania Vaglio, Domenico Prisco, Gianni Biancofiore, Daniela Rafanelli, PaolaAntonioli, Michele Lisanti, Lorenzo Andreani, Leonardo Basso, Claudio Velati, Giuliano Grazzini, Giancarlo Maria Liumbruno

Guida al buon uso degli emocomponenti, emoderivati e farmaci emostatici

9.1.3

La trasfusione in caso di anemia acuta nel periodo intraoperatorio dipende da vari fattori, fra cui la concentrazione di Hb, l'entità e la rapidità della perdita ematica, le condizioni cliniche del paziente (ovvero presenza di segni e sintomi di ipossia).

Si riportano di seguito i criteri decisionali per la trasfusione nell'anemia acuta in funzione della riduzione della volemia e dell'Hb, ricordando che valori di Hb < 6 g/dL rendono quasi sempre necessaria la terapia trasfusionale, mentre per valori compresi tra 6 e 10 g/dL, in pazienti stabilizzati, si rende necessaria la valutazione dello stato clinico (segni e sintomi di ipossia).

Una soglia restrittiva per la trasfusione (7 g/dL), rispetto ad una liberale (9 g/dL) è stata confermata una strategia efficace e sicura in pazienti con emorragie gastrointestinali acute.

Classificazione emorragia acuta	Perdite ematiche (mL)	Perdite ematiche (%)	Provvedimenti terapeutici	Grado Raccomandazione
Classe I	< 750	< 15	Soluzioni cristalloidi/colloidi CE non necessari, se non è preesistente un'anemia	2C+
Classe II	750 – 1500	15 – 30	Soluzioni cristalloidi/colloidi CE non necessari, se non è preesistente un'anemia e/o una malattia cardiopolmonare	2C+
Classe III	1500 – 2000	30 – 40	Soluzioni cristalloidi/colloidi Probabile necessità di trasfondere CE	2C+
Classe IV	> 2000	> 40	Infusione rapida di soluzioni cristalloidi/ colloidi e di CE	2C+

Eur J Anaesthesiol 2013; **30:**270–382

6.2.4.4 Transfusion triggers

Recommendation

We recommend a target haemoglobin concentration of 7–9 g dl^{-1} during active bleeding. **1C**

It has been demonstrated that acute anaemia (Hb < 5 g dl^{-1}) can be tolerated in healthy individuals, because compensatory mechanisms (predominantly an increase of cardiac output) can ensure sufficient tissue oxygenation.[296]

During bleeding, patients may be less able to tolerate anaemia because the compensatory mechanisms may be impaired. However, it is not known whether the lowest tolerable haemoglobin concentration is determined by volume status. Recent data from patients undergoing surgery and under intensive care indicate that a restrictive transfusion regimen (Hb 7–8 g dl^{-1}) is as effective and as safe as a liberal transfusion regimen (Hb 9–11 g dl^{-1}).[9,297–300] Considering the lack of benefits from higher haemoglobin concentrations, and the potential side effects of transfusing allogeneic blood, haemoglobin concentrations above 9 g dl^{-1} cannot be supported.[4]

Practice Guidelines for Perioperative Blood Management

*An Updated Report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management**

Anesthesiology 2015; 122:241-75

criteria for transfusion less than 8 g/dl and hematocrit values less than 25% are typically reported as restrictive.

Literature Findings: Meta-analysis of RCTs comparing restrictive with liberal transfusion criteria report fewer red blood cell transfusions when restrictive transfusion strategies are employed *(Category A1-B evidence).*[85–89] RCT findings for mortality, cardiac, neurologic or pulmonary complications, and length of hospital stay were equivocal *(Category A2-E evidence).*[85–93]

Survey Findings: The ASA members agree and the consultants strongly agree that a restrictive red blood cell transfusion strategy may be used to reduce transfusion requirements.

REVIEW

Red blood cell transfu
of anaemia: the searc

J. K. Wang & H. G. Klein

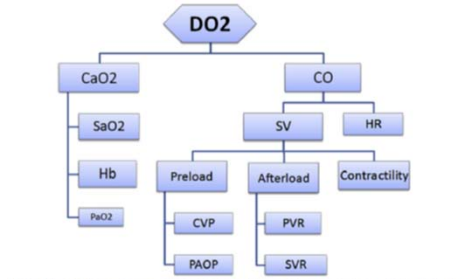

Fig. 2. Flowchart describing composition of the delivery of oxygen to tissues throughout the body. PVR, peripheric vascular resistance.

Global oxygen consumption (VO_2) which describes the amount of oxygen consumed by the whole body per minute ranges under physiological conditions in a normal adult from 200 to 300 ml/min whereas DO_2 ranges from 800 to 1200 ml/min. The relationship VO_2/DO_2 defines the oxygen extraction ratio (O_2ER) which is thus in the range of 20 to 30%. A normal VO_2/DO_2-relationship is illustrated in Figure 1. It

Arterial oxygen content	$CaO_2 = (Hb \times 1{\cdot}34 \times SaO_2) + (PaO_2 \times 0{\cdot}003)$
Oxygen delivery	$DO_2 = CO \times CaO_2$
Oxygen consumption	$VO_2 = CO \times (CaO_2 - CvO_2)$
	$VO_2 = CO \times ([Hb \times 1{\cdot}34 \times (SaO_2 - SvO_2)]$
	$+ [(PaO_2 - PvO_2) \times 0{\cdot}003])$
Oxygen extraction	$EO_2 = VO_2/DO_2$

REVIEW

Red blood cell transfu
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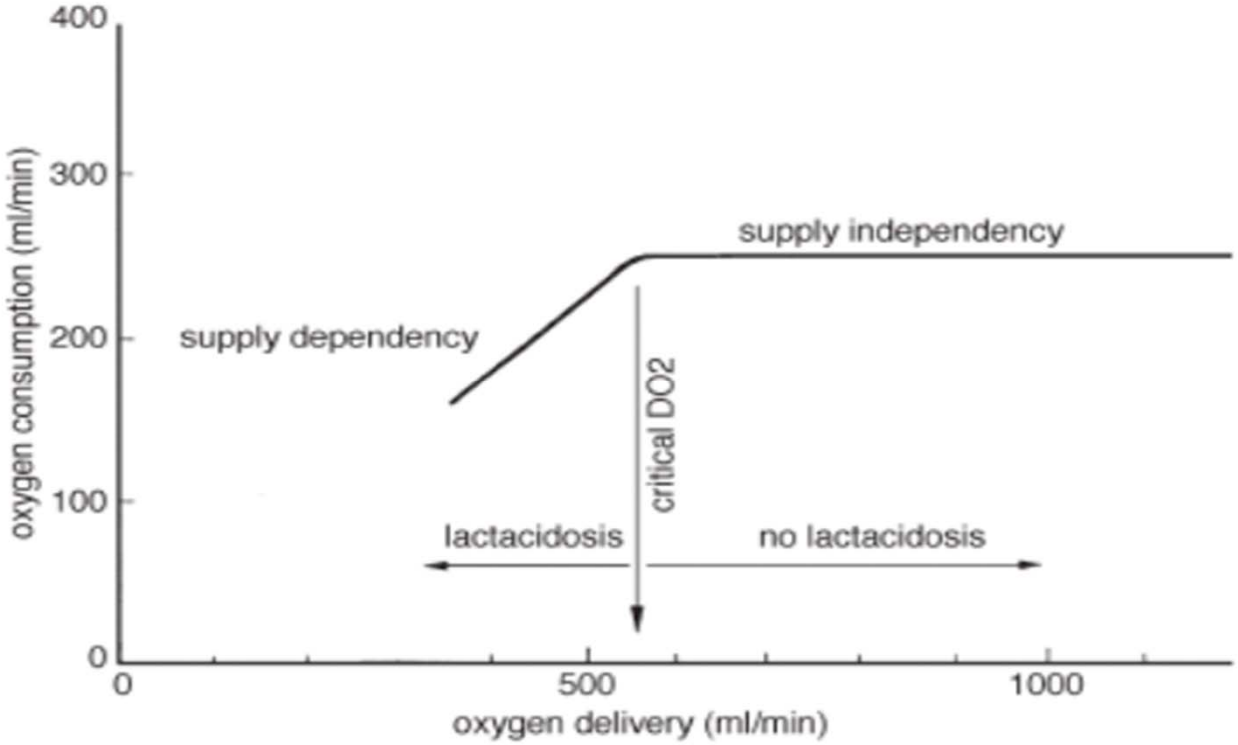

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	$+ [(PaO_2 - PvO_2) \times 0{\cdot}003])$
Oxygen extraction	$EO_2 = VO_2/DO_2$

Eur J Anaesthesiol 2013; **30:**270–382

6.2.3.1 Preload optimisation

Recommendation

We recommend aggressive and timely stabilisation of cardiac preload throughout the surgical procedure, as this appears beneficial to the patient. **1B**

Hypovolaemia decreases cardiac output and tissue oxygen supply. Both the extent and duration of tissue hypoperfusion determine the severity of cellular damage and should be kept to a minimum with timely

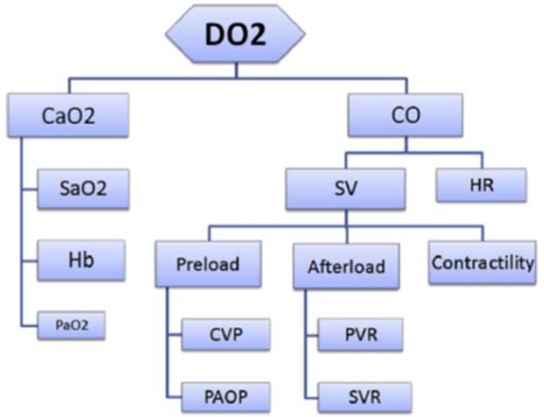


Fig. 2. Flowchart describing composition of the delivery of oxygen to tissues throughout the body. PVR, peripheric vascular resistance.

Recommendation

We recommend against the use of central venous pressure and pulmonary artery occlusion pressure as the only variables to guide fluid therapy and optimise preload during severe bleeding; dynamic assessment of fluid responsiveness and non-invasive measurement of cardiac output should be considered instead. **1B**

Volume expansion is important for the initial resuscitation of severe hypotension. Subsequent fluid administration should be given cautiously and only when there is evidence of fluid responsiveness to avoid fluid overload.[12] Indeed, several studies correlate excessive amounts of fluid (positive fluid balance) with increased mortality in acute respiratory distress syndrome or septic patients and failure of weaning from mechanical ventilation.[13–16] Moreover, only 50% of hemodynamically unstable patients are fluid responsive.[17,18]

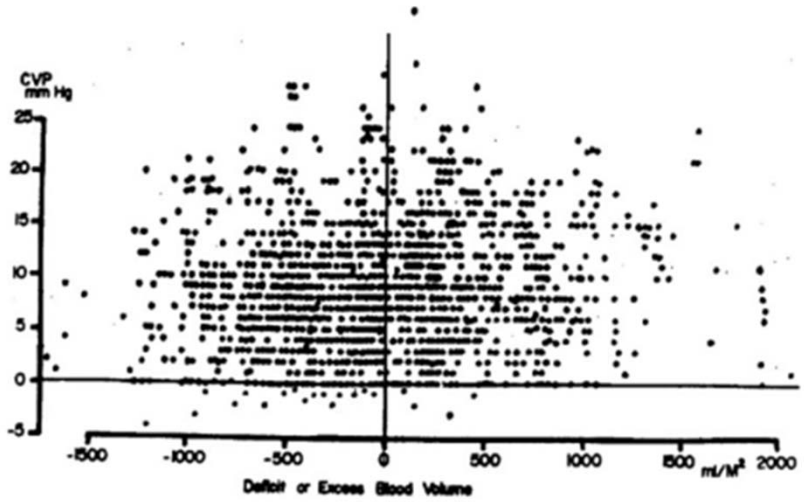
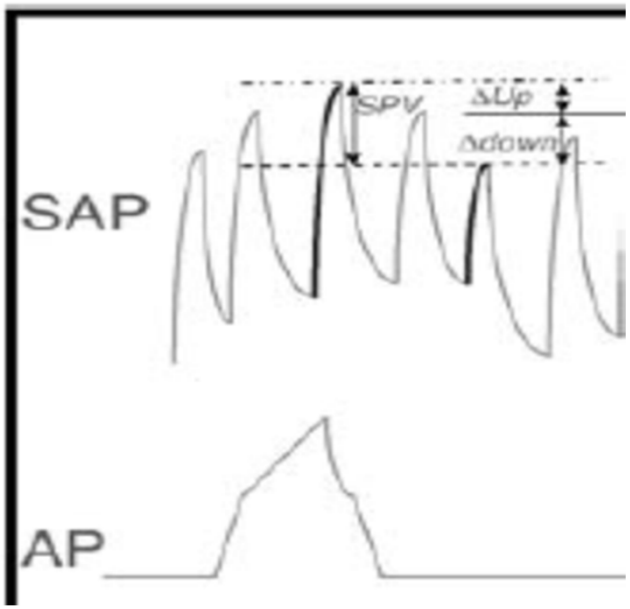


FIGURE 1. Fifteen hundred simultaneous measurements of blood volume and CVP in a heterogenous cohort of 188 ICU patients demonstrating no association between these two variables ($r = 0.27$). The correlation between ΔCVP and change in blood volume was 0.1 ($r^2 = 0.01$). This study demonstrates that patients with a low CVP may have volume overload and likewise patients with a high CVP may be volume depleted. Reproduced with permission from Shippy et al.[11]

In contrast to static preload measures, which only rely on hemodynamic values at a given point in time, there are newer dynamic parameters currently available using the change in SV during mechanical ventilation to assess fluid responsiveness. New noninvasive CO monitoring is available today to measure or estimate CO, pulse pressure variation, or SV variation. Resuscitation should, of course, target normalization of



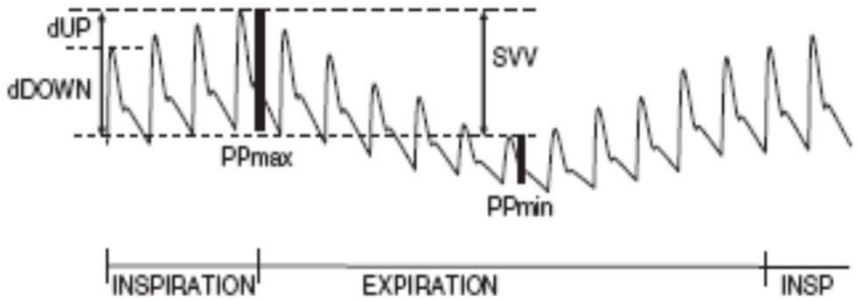


FIGURE 5. Relationship of arterial pressure wave and passive respiration. Compared to end-expiration, the systolic pressure and pulse pressure rise during inspiration (INSP), then fall during expiration. PPmax = maximal pulse pressure; PPmin = minimal pulse pressure.

Annals of Intensive Care 2011, **1**:1

REVIEW Open Access

Hemodynamic parameters to guide fluid therapy

Paul E Marik[1*], Xavier Monnet[2], Jean-Louis Teboul[2]

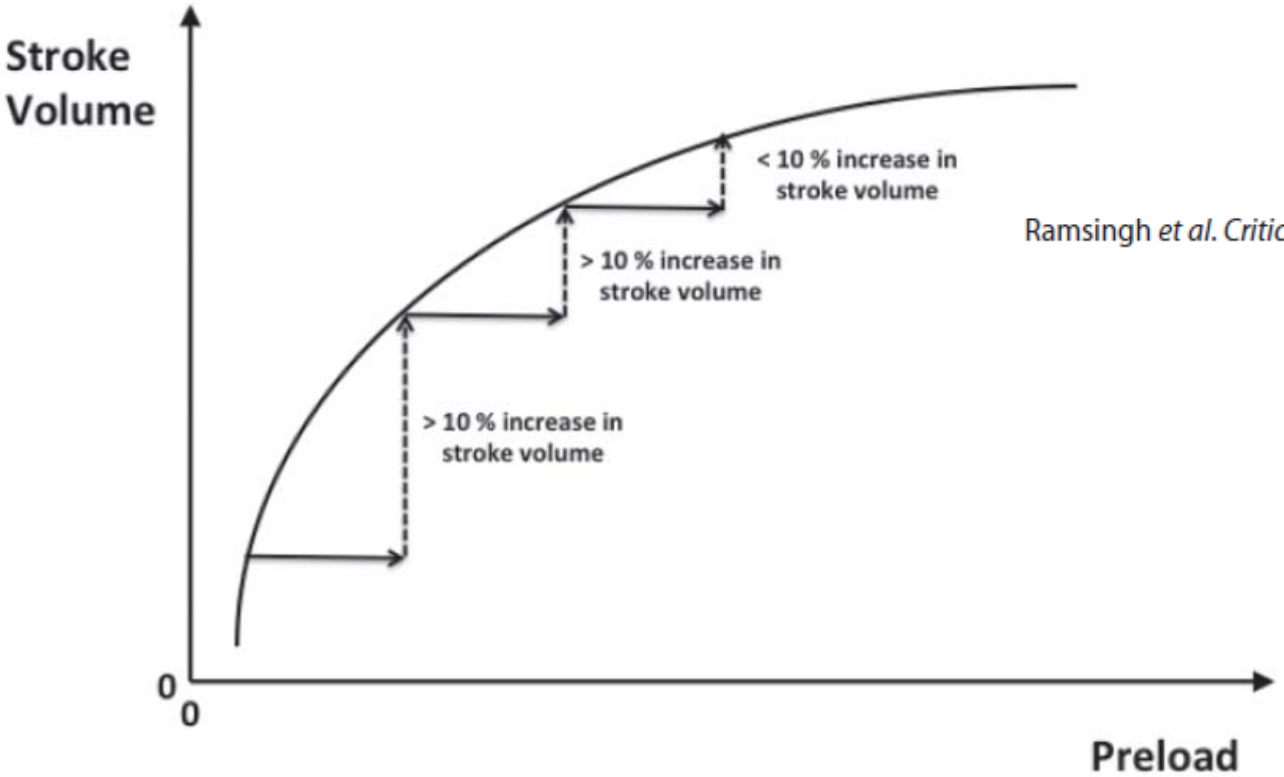
Table 2 Predictive value of techniques used to determine fluid responsiveness [15]

Method	Technology	AUC*
Pulse pressure variation (PPV)	Arterial waveform	0.94 (0.93-0.95)
Systolic pressure variation (SPV)	Arterial waveform	0.86 (0.82-0.90)
Stroke volume variation (SVV)	Pulse contour analysis	0.84 (0.78-0.88)
Left ventricular end-diastolic area (LVEDA)	Echocardiography	0.64 (0.53-0.74)
Global end-diastolic volume (GEDV)	Transpulmonary thermodilution	0.56 (0.37-0.67)
Central venous pressure (CVP)	Central venous catheter	0.55 (0.48-0.62)

*AUC = area under the curve with 95% confidence intervals.

Variations in PPV, SVV $\geq$10–13% and PVI $\geq$15% are highly predictive of preload responsiveness. SVV, PPV and PVI are unreliable in the presence of spontaneous breathing, cardiac arrhythmia, open chest, tidal volume <7 ml kg^{-1}, intra-abdominal hypertension and right ventricular failure [67,68], and end-expiratory

C'est l'augmentation du VES en réponse au remplissage qui confirme que le RV réalisé était pertinent et autorise une poursuite de celui-ci. La valeur absolue du VES mesurée par les outils de monitorage (quels qu'ils soient) n'est pas un critère absolu pour décider de l'opportunité d'un remplissage ou de sa poursuite. En effet, une valeur « normale » ou « élevée » du VES ne préjuge pas de son caractère adapté aux besoins ni de l'absence d'une élévation du VES en réponse au test de remplissage.



Ramsingh *et al. Critical Care* 2013, 17:208

Figure 1. Fluid optimization concept based on stroke volume monitoring. The concept of cardiac output maximization based on fluid administration and stroke volume monitoring. Small boluses of fluid are administered intravenously (200 to 250 ml at a time) until the stroke

N ENGL J MED 369;13 NEJM.ORG SEPTEMBER 26, 2013

Resuscitation Fluids

John A. Myburgh, M.B., B.Ch., Ph.D., and Michael G. Mythen, M.D., M.B., B.S.

THE IDEAL RESUSCITATION FLUID

The ideal resuscitation fluid should be one that produces a predictable and sustained increase in intravascular volume, has a chemical composition as close as possible to that of extracellular fluid, is metabolized and completely excreted without accumulation in tissues, does not produce adverse metabolic or systemic effects, and is cost-effective in terms of improving patient outcomes. Currently, there is no such fluid available for clinical use.

Colloid solutions are suspensions of molecules within a carrier solution that are relatively incapable of crossing the healthy semipermeable capillary membrane owing to the molecular weight of the molecules. Crystalloids are solutions of ions that are freely permeable but contain concentrations of sodium and chloride that determine the tonicity of the fluid.

Fluid Composition and Clinical Effects

Crit Care Clin 31 (2015) 823–837

Matt Varrier, MBBS, MRCP, Marlies Ostermann, PhD, MD, FRCP, EDIC*

Crystalloids

Crystalloids are aqueous solutions containing minerals and/or salts of organic acids. They differ in electrolyte composition, pH, osmolarity, effect on acid base status, and strong ion difference and can be divided into balanced and unbalanced solutions based on their similarity with plasma[7] (**Table 1**).

Table 1. Electrolyte composition (mmol/l) of commonly available crystalloids

Electrolyte	Plasma	0.9% NaCl	Ringer's lactate, Hartmann's	Plasma-Lyte®	Sterofundin®
Sodium	140	154	131	140	140
Potassium	5	0	5	5	4
Chloride	100	154	111	98	127
Calcium	2.2	0	2	0	2.5
Magnesium	1	0	1	1.5	1
Bicarbonate	24	0	0	0	0
Lactate	1	0	29	0	0
Acetate	0	0	0	27	24
Gluconate	0	0	0	23	0
Maleate	0	0	0	0	5

Plasma-Lyte® from Baxter International (Deerfield, IL, USA). Sterofundin® from B Braun (Melsungen, Germany).

0.9% Sodium chloride Saline 0.9% is the most commonly used fluid worldwide. After infusion, it is rapidly distributed between the compartments of the extracellular space. In health, approximately 60% of the infused volume diffuses from the intravascular space into the interstitial compartment within 20 minutes of administration.[8] These fluid shifts are even faster in conditions associated with endothelial dysfunction.

NaCl 0.9% has a nonphysiologic ion content and supraphysiologic concentration of chloride (see **Table 1**). As a result, administration of 0.9% NaCl can lead to hyperchloremia and metabolic acidosis.

Balanced crystalloids

Balanced crystalloids are solutions with an ionic composition more similar to plasma than 0.9% NaCl. Several types are commercially available. They differ in their ionic makeup, osmolarity, tonicity, and type of metabolizable anion, such as acetate, lactate, and malate (see **Table 1**).

Ringer lactate solution has an osmolarity of 273 mosmol/L and can cause a small reduction in plasma osmolality.

Hartmann's solution is a slightly modified form of Ringer lactate.

Plasma-Lyte and Sterofundin contain electrolytes in concentrations that are more similar to plasma compared with Hartmann and Ringer lactate (see **Table 1**).

What is the ideal crystalloid?

Curr Opin Crit Care 2015, 21:309–314

Karthik Raghunathan[a], *Patrick Nailer*[b], *and Ryan Konoske*[a]

Chloride load

Chloride-liberal solutions, like isotonic saline, have been associated with the predictable development of hyperchloremic metabolic acidosis with subsequently impaired renal perfusion (via renal vasoconstriction and renal cortical hypoperfusion) [9], impairment of immune function [10], and potentially decreased in-hospital survival [2▪▪]. Among patients undergoing major abdominal surgery, saline has been associated with increased acute renal failure and in-hospital mortality when compared with Plasma-Lyte in a large study using claims data [11].

PRELIMINARY COMMUNICATION

Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

Nor'azim Mohd Yunos, MD
Rinaldo Bellomo, MD, FCICM
Colin Hegarty, BSc
David Story, MD
Lisa Ho, MClinPharm
Michael Bailey, PhD

Context Administration of traditional chloride-liberal intravenous fluids may precipitate acute kidney injury (AKI).

Objective To assess the association of a chloride-restrictive (vs chloride-liberal) intravenous fluid strategy with AKI in critically ill patients.

Design, Setting, and Patients Prospective, open-label, sequential period pilot study of 760 patients admitted consecutively to the intensive care unit (ICU) during the control period (February 18 to August 17, 2008) compared with 773 patients admitted consecutively during the intervention period (February 18 to August 17, 2009) at a university-affiliated hospital in Melbourne, Australia.

Interventions During the control period, patients received standard intravenous fluids. After a 6-month phase-out period (August 18, 2008, to February 17, 2009), any use of chloride-rich intravenous fluids (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution) was restricted to attending specialist approval only during the intervention period; patients instead received a lactated solution (Hartmann solution), a balanced solution (Plasma-Lyte 148), and chloride-poor 20% albumin.

Main Outcome Measures The primary outcomes included increase from baseline to peak creatinine level in the ICU and incidence of AKI according to the risk, injury, failure, loss, end-stage (RIFLE) classification. Secondary post hoc analysis outcomes included the need for renal replacement therapy (RRT), length of stay in ICU and hospital, and survival.

Results Chloride administration decreased by 144 504 mmol (from 694 to 496 mmol/patient) from the control period to the intervention period. Comparing the control period with the intervention period, the mean serum creatinine level increase while in the ICU was 22.6 μmol/L (95% CI, 17.5-27.7 μmol/L) vs 14.8 μmol/L (95% CI, 9.8-19.9 μmol/L) (P=.03), the incidence of injury and failure class of RIFLE-defined AKI was 14% (95% CI, 11%-16%; n=105) vs 8.4% (95% CI, 6.4%-10%; n=65) (P<.001), and the use of RRT was 10% (95% CI, 8.1%-12%; n=78) vs 6.3% (95% CI, 4.6%-8.1%; n=49) (P=.005). After adjustment for covariates, this association remained for incidence of injury and failure class of RIFLE-defined AKI (odds ratio, 0.52 [95% CI, 0.37-0.75]; P<.001) and use of RRT (odds ratio, 0.52 [95% CI, 0.33-0.81]; P=.004). There were no differences in hospital mortality, hospital or ICU length of stay, or need for RRT after hospital discharge.

Conclusion The implementation of a chloride-restrictive strategy in a tertiary ICU was associated with a significant decrease in the incidence of AKI and use of RRT.

Trial Registration clinicaltrials.gov Identifier: NCT00885404

JAMA. 2012;308(15):1566-1572 www.jama.com

Significance of Study Findings

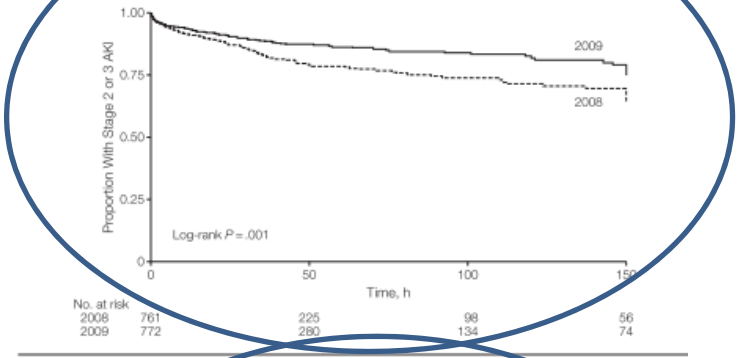
The findings of this study show that a chloride-restrictive intravenous strategy is associated with a decrease in the incidence of the more severe stages of AKI and the use of RRT. These findings, together with the previously reported observations that a chloride-liberal intravenous strategy can be associated with higher cost,[6] and the easy availability of cheap alternatives suggest the need to exert prudence in the administration of fluids with supraphysiological concentrations of chloride, especially in critically ill patients with evidence of early acute renal dysfunction or at risk of acute dysfunction.

Table 3. Incidence of Acute Kidney Injury Stratified by Risk, Injury, Failure, Loss, and End-Stage (RIFLE) Serum Creatinine Criteria

	No. (%) [95% CI] of Patients[a]		
	Control Period (n = 760)	Intervention Period (n = 773)	*P* Value
RIFLE class			
Risk	71 (9.0) [7.2-11.0]	57 (7.4) [5.5-9.0]	.16
Injury	48 (6.3) [4.5-8.1]	23 (3.0) [1.8-4.2]	.002
Failure	57 (7.5) [5.6-9.0]	42 (5.4) [3.8-7.1]	.10
Injury and failure	105 (14) [11-16]	65 (8.4) [6.4-10.0]	<.001

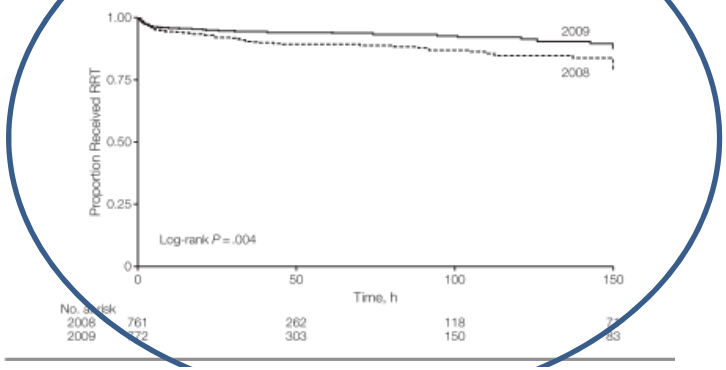
[a]The control period was from February 18 through August 17, 2008, and the intervention period was from February 18 through August 17, 2009.

Figure 1. Development of Stage 2 or 3 Acute Kidney Injury (AKI) While in the Intensive Care Unit (ICU)



Stage 2 or 3 defined according to the Kidney Disease: Improving Global Outcomes clinical practice guideline

Figure 2. Renal Replacement Therapy (RRT) in the Intensive Care Unit (ICU)



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British Journal of Anaesthesia **112** (6): 968–81 (2014)
Advance Access publication 15 April 2014 · doi:10.1093/bja/aeu047

BJA

REVIEW ARTICLES

Isotonic crystalloid solutions: a structured review of the literature

D. Orbegozo Cortés, A. Rayo Bonor and J. L. Vincent*

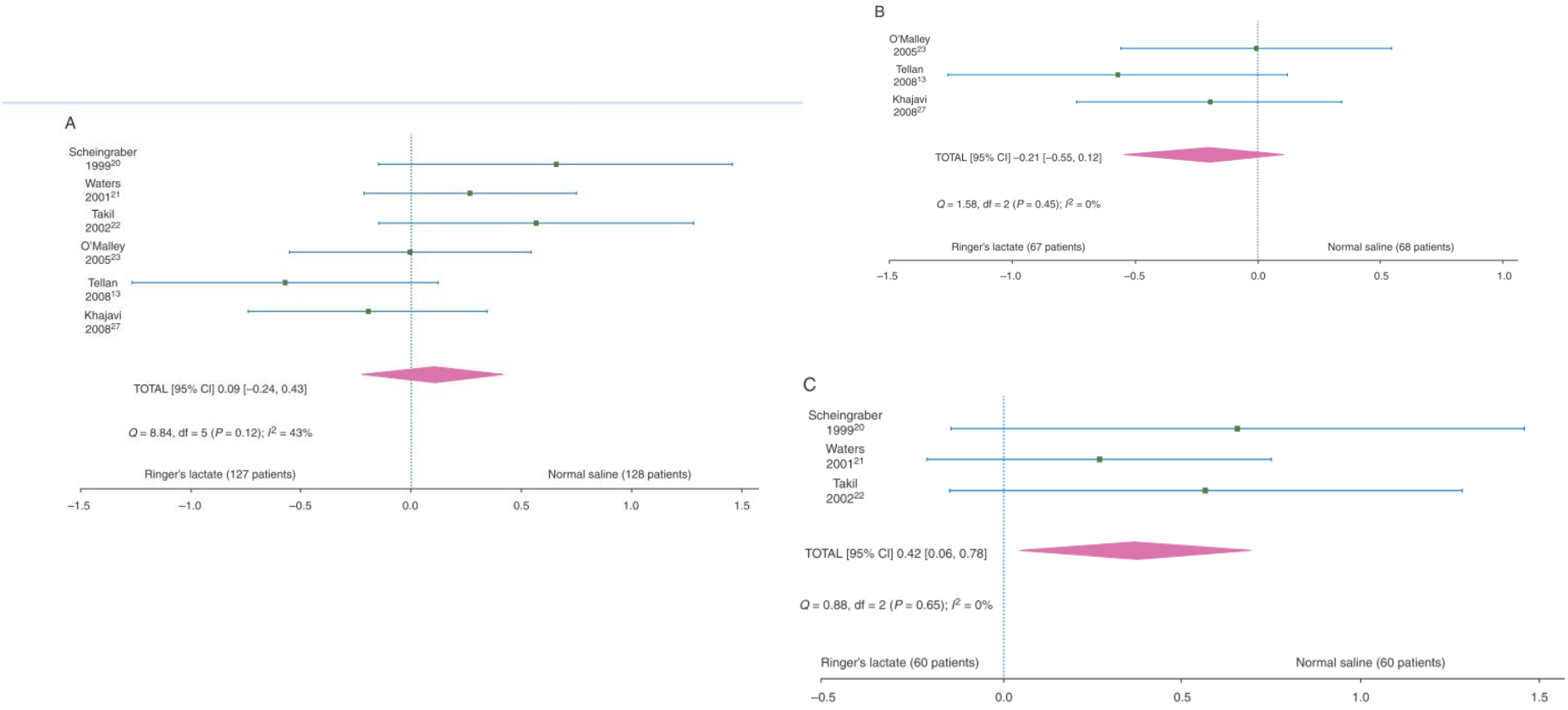


Fig 4 Forest plot of blood loss volumes in studies comparing normal saline with Ringer's lactate when considering all patients (A), patients with a low risk of bleeding (B), and patients with a high risk of bleeding (C).

Fluid Management in Abdominal Surgery

What, When, and When Not to Administer

Anesthesiology Clin 33 (2015) 51–64

Karthik Raghunathan, MD, MPH[a,*], Mandeep Singh, MD[b],
Dileep N. Lobo, MS, DM, FRCS, FACS, FRCPE[c]

Elevated serum chloride concentrations have been associated with renal vasoconstriction and renal parenchymal swelling in animal studies[8,9] and an increase in postoperative 30-day mortality in large database analyses.[10] The deleterious effects of administration of large volumes of 0.9% saline on the kidney have also been shown in a human study that demonstrated decreased renal blood flow velocity and cortical tissue perfusion.[11] Acknowledging potential clinical implications, the British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients recommended the use of balanced crystalloids rather than isotonic saline in most routine clinical settings.[12] The case for balanced crystalloids has also been presented comprehensively in a review.[13]

Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit
The SPLIT Randomized Clinical Trial

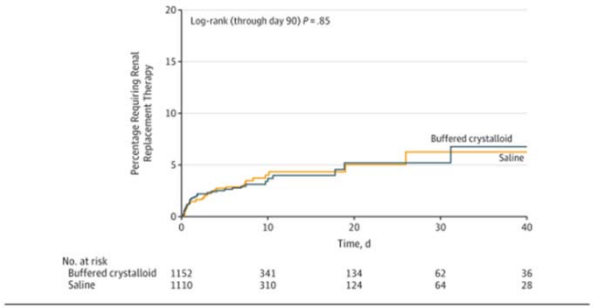
JAMA. doi:10.1001/jama.2015.12334
Published online October 7, 2015.

Paul Young, FCICM; Michael Bailey, PhD; Richard Beasley, DSc; Seton Henderson, FCICM; Diane Mackle, MN; Colin McArthur, FCICM; Shay McGuinness, FANZCA; Jan Mehrtens, RN; John Myburgh, PhD; Alex Psirides, FCICM; Sumeet Reddy, MBChB; Rinaldo Bellomo, FCICM; for the SPLIT Investigators and the ANZICS CTG

INTERVENTIONS Participating ICUs were assigned a masked study fluid, either saline or a buffered crystalloid, for alternating 7-week treatment blocks. Two ICUs commenced using 1 fluid and the other 2 commenced using the alternative fluid. Two crossovers occurred so that 8 weeks of the study. The treating clinician id administration.

mary outcome was proportion of patients with AKI l of at least 2-fold or a serum creatinine level of g/dL); main secondary outcomes were incidence of

Figure 2. Cumulative Incidence of Patients Requiring Renal Replacement Therapy Until Day 90 After Enrollment in the SPLIT Trial



Censoring applied at hospital discharge or death. The x-axis is truncated at 40 days because the number of participants still in follow-up beyond 40 days is small.

, 102 of 1067 patients (9.6%) developed AKI within 94 of 1025 patients (9.2%) in the saline group (absolute difference, 0.4% [95% CI, −2.1% to 2.9%]; relative risk [RR], 1.04 [95% CI, 0.80 to 1.36]; P = .77). In the buffered crystalloid group, RRT was used in 38 of 1152 patients (3.3%) compared with 38 of 1110 patients (3.4%) in the saline group (absolute difference, −0.1% [95% CI, −1.6% to 1.4%]; RR, 0.96 [95% CI, 0.62 to 1.50]; P = .91). Overall, 87 of 1152 patients (7.6%) in the buffered crystalloid group and 95 of 1110 patients (8.6%) in the saline group died in the hospital (absolute difference, −1.0% [95% CI, −3.3% to 1.2%]; RR, 0.88 [95% CI, 0.67 to 1.17]; P = .40).

CONCLUSIONS AND RELEVANCE Among patients receiving crystalloid fluid therapy in the ICU, use of a buffered crystalloid compared with saline did not reduce the risk of AKI. Further large randomized clinical trials are needed to assess efficacy in higher-risk populations and to measure clinical outcomes such as mortality.

What is the ideal crystalloid?

Karthik Raghunathan[a], *Patrick Nailer*[b], *and Ryan Konoske*[a]

Curr Opin Crit Care 2015, 21:309–314

When the goal of therapy is to correct dehydration and hypochloremic alkalosis (this might occur from prolonged vomiting or nasogastric suctioning), isotonic saline is appropriate. Similarly, Plasma-Lyte may be appropriate for coadministration with blood products when there is significant blood loss, thereby avoiding both the risk of precipitation of citrate and hyperchloremic acidosis.

Fluid Composition and Clinical Effects

Matt Varrier, MBBS, MRCP, Marlies Ostermann, PhD, MD, FRCP, EDIC*

Colloids

Colloids are crystalloid solutions containing oncotic macromolecules that largely remain in the intravascular space and, thereby, generate an oncotic pressure

polydispersity. Following infusion, the net effect depends on the type of colloid, the concentration, the distribution of its molecular weight (MW), and the crystalloid carrier.

Large molecules have restricted movement across the capillary wall. By acting as effective osmoles, they keep water in the intravascular space and prevent free movement into the interstitial space (oncotic pressure) (see **Table 2**). In contrast, small solutes move rapidly into the extravascular space in response to a concentration gradient and/or hydrostatic pressure. In health, a low concentration of protein is also found in the interstitium, which exerts a small tissue oncotic pressure.

IMPORTANT PROPERTIES OF COLLOIDS

Molecular Weight

Large molecules have a greater oncotic effect and may take longer to be metabolized and eliminated and, therefore, lengthen the duration of action. Smaller molecules may be cleared faster and are also more permeable across the capillary wall. The oncotic effects are dynamic as larger molecules may be broken down to smaller molecules with differing properties.[10]

Oncotic Pressure

The oncotic pressure generated by a colloid is primarily determined by the MW and concentration (Table 3). Hyperoncotic preparations (eg, albumin 20%) expand the plasma volume by more than the volume infused.[11]

Metabolism, Elimination, and Duration of Effect

The body handles each type of colloid differently, and the plasma half-lives vary greatly (see Table 3). In general, larger molecules take longer to be metabolized and have a longer duration of action, especially if their metabolites are also osmotically active. Smaller molecules less than the glomerular threshold of 60 kDa are excreted in the urine, provided the renal function is intact.

Carrier Fluid

All colloids are carried in a crystalloid solution. Commonly this is NaCl based, although balanced colloids are available (see Table 3). The carrier solution has similar effects to when infused alone (eg, hyperchloremic metabolic acidosis in the case of 0.9% NaCl). The degree to which this occurs depends on the volume, rate, and underlying physiology.

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Intravascular Volume Replacement Therapy with Synthetic Colloids: Is There an Influence on Renal Function?

Joachim Boldt, MD*, and Hans-Joachim Priebe, FRCA†

Table 1. Characteristics of the Different Colloids

Variable	Albumin 5%	Albumin 20%/25%	HES 70/0.5	HES 130/0.4	HES 200/0.5	HES 200/0.5	HES 200/0.62	HES 450/0.7	Dextran 60	Dextran 40	Gelatins
Concentration (%)	5	20/25	6	6	6	10	6	6	6	10	3.5–5.5
Volume efficacy (%)	80	130–150	80	100	100	130–150	100	100	100	150–200	80
Volume effect (h)	Short (2–3)	Short (2–3)	Short (1–2)	Short (2–3)	Medium (3–4)	Medium (3–4)	Long (5–6)	Long (5–6)	Long (5)	Medium (3–4)	Short (1–2)
Mean molecular weight (kd)	69	69	70	130	200	200	200	450	60	40	30–35
Degree of substitution			0.5	0.4	0.5	0.5	0.62	0.7			
C2/C6 ratio			4:1	9:1	6:1	6:1	9:1	4.6:1			

HES = hydroxyethyl starch.

Colloids

Colloids are crystalloid solutions containing oncotic macromolecules that largely remain in the intravascular space and, thereby, generate an oncotic pressure

Table 2. Electrolyte composition (mmol/l) of commonly available colloids

	Albumin 4%	Plasmion® Geloplasma®	Gelofusine®	Voluven® (waxy maize HES 6% 130/0.40)	Venofundin® (potato HES 6% 130/0.42)	Hextend® (waxy maize HES 6% 670/0.75)	Volulyte® (waxy maize HES 6% 130/0.40)	PlasmaVolume® (potato HES 6% 130/0.42)	Tetraspan® (potato HES 6% 130/0.42)
Sodium	140	150	154	154	154	143	137	130	140
Potassium	0	5	0	0	0	3	4	5.4	4.0
Chloride	128	100	125	154	154	124	110	112	118
Calcium	0	0	0	0	0	2.5	0	0.9	2.5
Magnesium	0	1.5	0	0	0	0.5	1.5	1	1.0
Bicarbonate	0	0	0	0	0	0	0	0	0
Lactate	0	30	0	0	0	28	0	0	0
Acetate	0	0	0	0	0	0	34	27	24
Malate	0	0	0	0	0	0	0	0	5
Octanoate	6.4	0	0	0	0	0	0	0	0

HES, hydroxyethyl starch. Gelofusine®, Venofundin® and Tetraspan® from B Braun (Melsungen, Germany). Plasmion®, Geloplasma®, Voluven® and Volulyte® from Fresenius-Kabi (Bad Homburg, Germany). Hextend® from BioTime Inc. (Berkeley, CA, USA). PlasmaVolume® from Baxter International (Deerfield, IL, USA).

CAN J ANESTH 2006 / 53: 6 / pp S30–S39

The effects of colloid solutions on hemostasis

[Les effets des solutions colloïdes sur l'hémostase]

Philippe Van der Linden MD PhD,* Brigitte E. Ickx MD†

Biological effects

Albumin inhibits platelet aggregation directly.[12] In contrast to synthetic colloids, albumin does not have a coating effect on platelets.[16] *In vitro*, albumin might also alter fibrin polymerization,[17] without apparent physiological consequences. *In vivo*, albumin does not appear to have specific effects on hemostatic components, except those related to hemodilution.[16,18] These effects appear significant only when hemodilution becomes profound (blood volume exchange above 30%).[19,20]

Clinical effects

Several clinical studies, in cardiac, orthopedic and urologic surgery and in the intensive care unit, have evaluated the effects of synthetic colloids on perioperative hemostasis, using albumin as the substitute of reference. In none of these studies has albumin been associated with bleeding greater than with synthetic colloids.[16,21–23] Consequently, albumin is considered as a colloid devoid of any specific effect on hemostasis.

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The effects of colloid solutions on hemostasis

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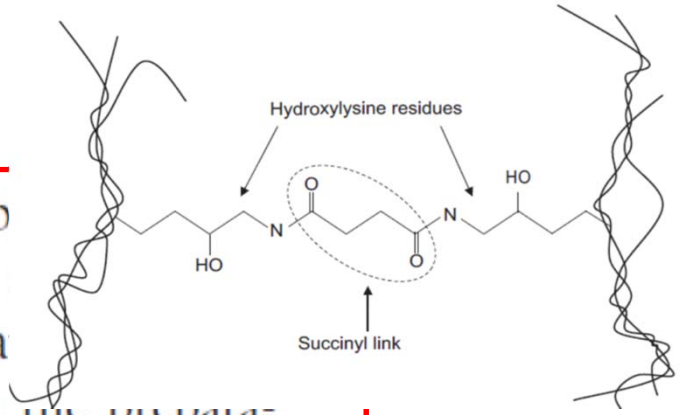
Gelatins

Pharmacology

Gelatins are polypeptides obtained b
of bovine collagen.[33] The addition of
anhydride leads to profound modifica
polypeptide's conformation resulting in
tion of "fluid modified gelatins". The cross-linking of the raw polypeptides by the addition of hexamethyl di-isocyanate results in the preparation of "urea-linked gelatins". Concentrations of the different gelatin solutions available commercially vary from 3.0 to 4.0



Commonly Used Gelatin Preparations

Gelatins	MW (kDa)	Duration (hours)	Na^+	Cl^-	K^+	Ca^{2+}	Major Risks
Urea-bridged	35	2-3	145	145	5.1	6.26	Allergy
Modified Fluid	35	2-3	154	125	0.4	0.	Lower allergic risk

Clinical Relevance of the Effects of Plasma Expanders on Coagulation

Marcel Levi, M.D., Ph.D., F.R.C.P.,[1] and Evert de Jonge, M.D., Ph.D.[2]

Although for a long time gelatins were considered not to influence blood coagulation other than by dilution,[6] there is now increasing evidence that gelatins do influence platelet function and blood coagulation.

Semin Thromb Hemost 2007;33:810–815.

Mardel SN, Saunders FM, Allen H, et al. Reduced quality of clot formation with gelatin-based plasma substitutes. Br J Anaesth 1998;80:204–207

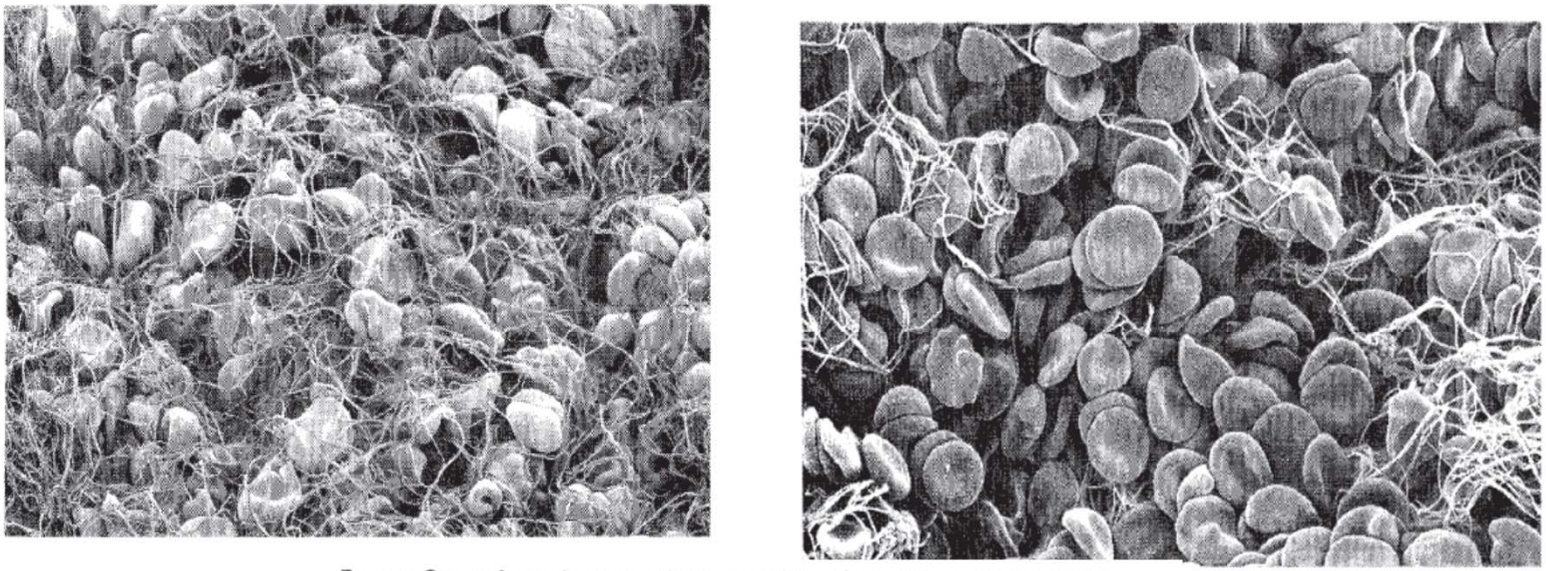


Figure: **Scanning electromicrographs of whole blood (top) diluted to 66% with 0·9% sodium chloride and (bottom) with succinylated gelatin**

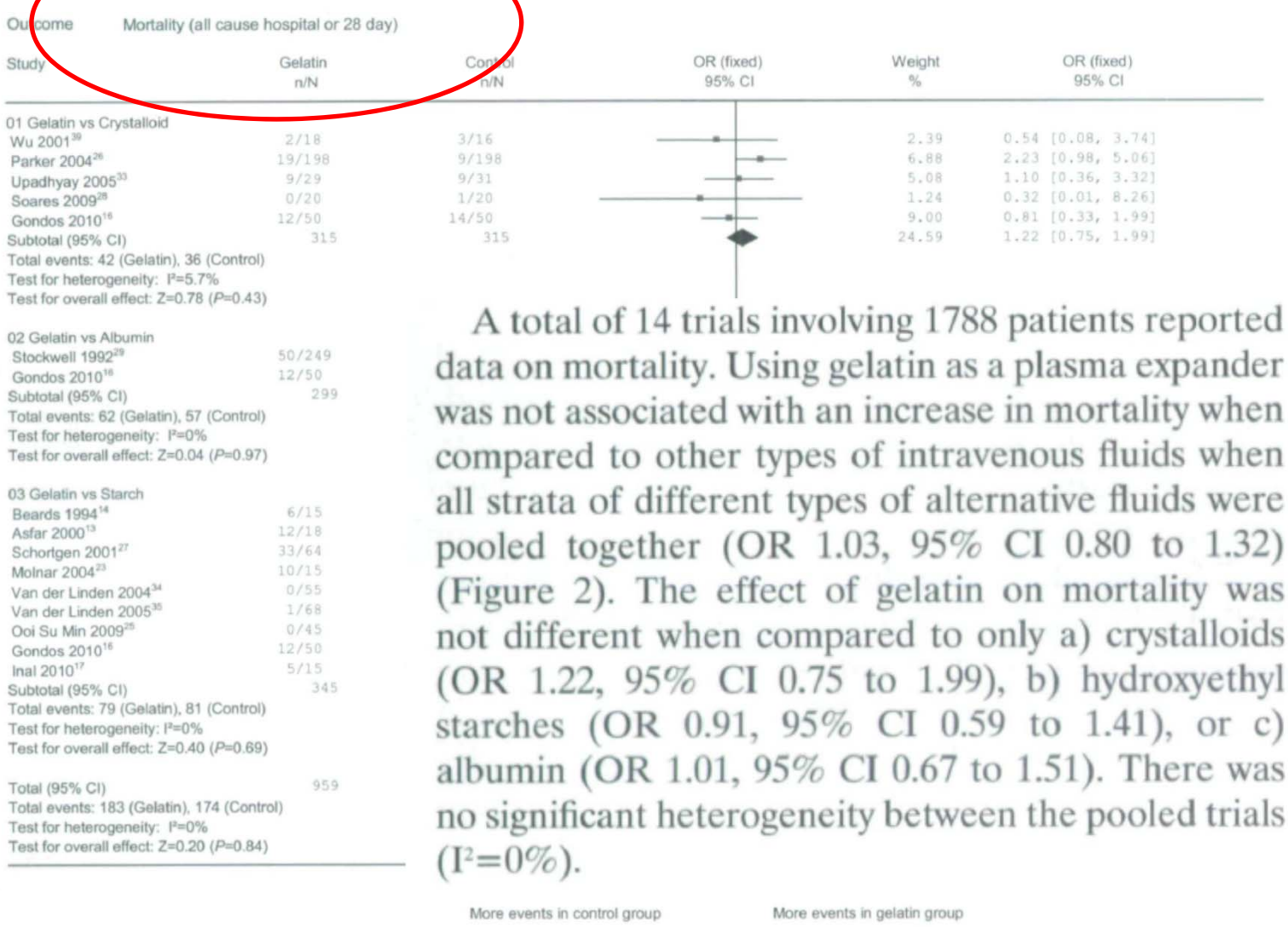
microscopy. The widespread mesh pattern of fibrin strands seen in normal blood clot was retained in the 0·9% saline control (figure, top), while this reticular network was much reduced in clots containing gelatin colloids (figure, bottom).

Anaesth Intensive Care 2012; 40: 17-32

Reviews

Benefits and risks of using gelatin solution as a plasma expander for perioperative and critically ill patients: a meta-analysis

M. M. SAW*, B. CHANDLER†, K. M. HO‡



A total of 14 trials involving 1788 patients reported data on mortality. Using gelatin as a plasma expander was not associated with an increase in mortality when compared to other types of intravenous fluids when all strata of different types of alternative fluids were pooled together (OR 1.03, 95% CI 0.80 to 1.32) (Figure 2). The effect of gelatin on mortality was not different when compared to only a) crystalloids (OR 1.22, 95% CI 0.75 to 1.99), b) hydroxyethyl starches (OR 0.91, 95% CI 0.59 to 1.41), or c) albumin (OR 1.01, 95% CI 0.67 to 1.51). There was no significant heterogeneity between the pooled trials (I^2=0%).

Anaesth Intensive Care 2012; 40: 17-32

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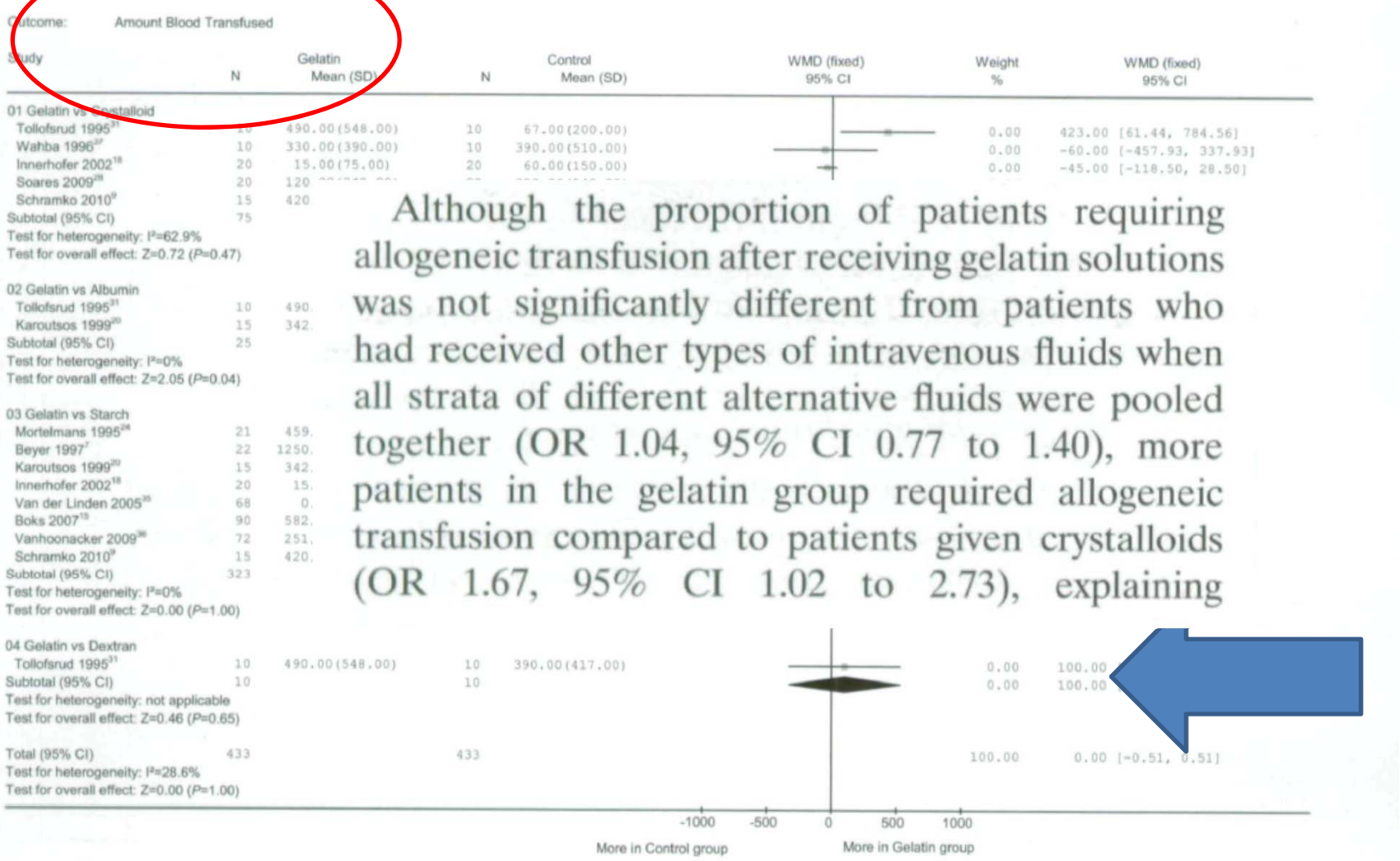
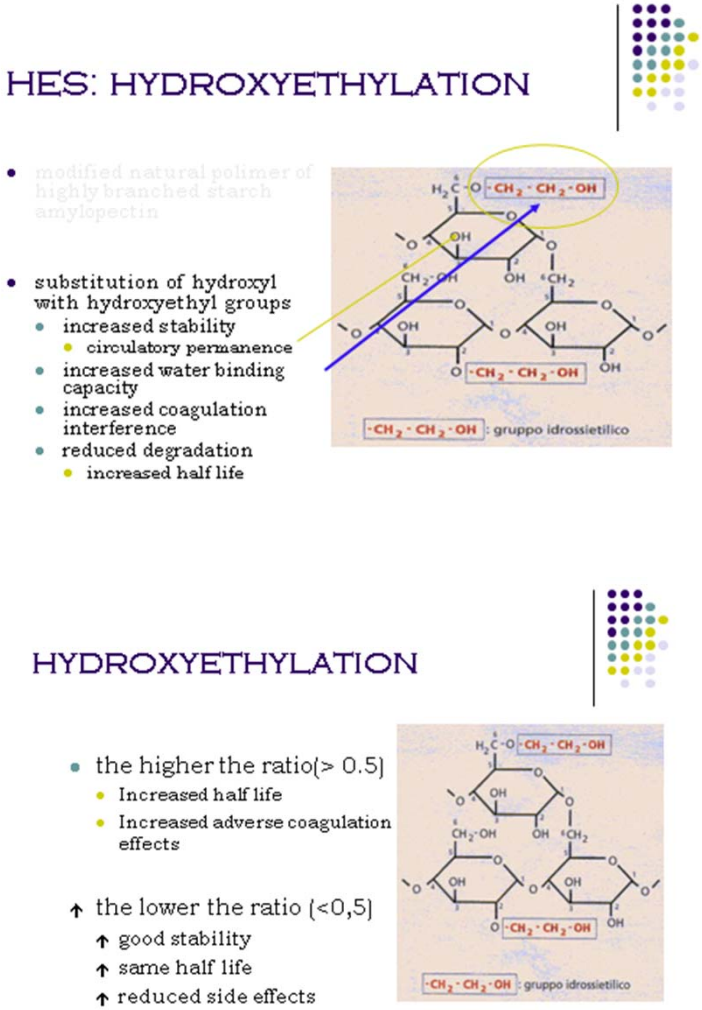


Although the proportion of patients requiring allogeneic transfusion after receiving gelatin solutions was not significantly different from patients who had received other types of intravenous fluids when all strata of different alternative fluids were pooled together (OR 1.04, 95% CI 0.77 to 1.40), more patients in the gelatin group required allogeneic transfusion compared to patients given crystalloids (OR 1.67, 95% CI 1.02 to 2.73), explaining

Idrossietilamidi (HES)

1 the molar substitution (mol hydroxyethyl residues per mol glucose subunit) into hetastarch (highly substituted: 0.62–0.75), pentastarch (medium substituted: 0.5) and tetrastarch (low substituted: 0.4),
2 the C2/C6 ratio (pattern of hydroxyethylation at the carbon position C2 and C6) into solutions with a high C2/C6 ratio (> 8) and low C2/C6 ratio (< 8), and
3 the manufactured mean molecular weight into high-molecular-weight (450–670 kD), medium-molecular-weight (130, 200 kD) and low-molecular-weight solutions (< 70 kD).



Principles of perioperative coagulopathy

Petra Innerhofer, MD, Assoc. Prof. [a,*], Joachim Kienast, MD, Assoc. Prof. [b]

The induction of a von Willebrand-like syndrome has been observed in patients receiving HES solutions, and a significant decrease in von Willebrand Ristocetin activity (localised at the high molecular part of the vWF, permits platelet adhesion to the endothelium and between each other) was also observed following infusion of gelatine.[65,66] However, it can be assumed that, in most surgical patients, these effects are minor when using the rapidly degradable new HES solution at recommended doses. By contrast, in patients showing borderline vWF activity or repeatedly receiving highly substituted high-molecular-weight HES over several days, severe bleeding can be provoked.[67] Although gelatin, HES130/0.4 and HES 200/0.5 showed no influence on endogenous release of molecular markers of fibrinolysis *in vivo*, a decreased resistance of clots to fibrinolysis has been observed with colloids *in vitro*.[68,69] This might refer to colloid-associated interference with FXIII or to the fact that weaker clots dissolve faster.[70,71]

Best Practice & Research Clinical Anaesthesiology 24 (2010) 1–14

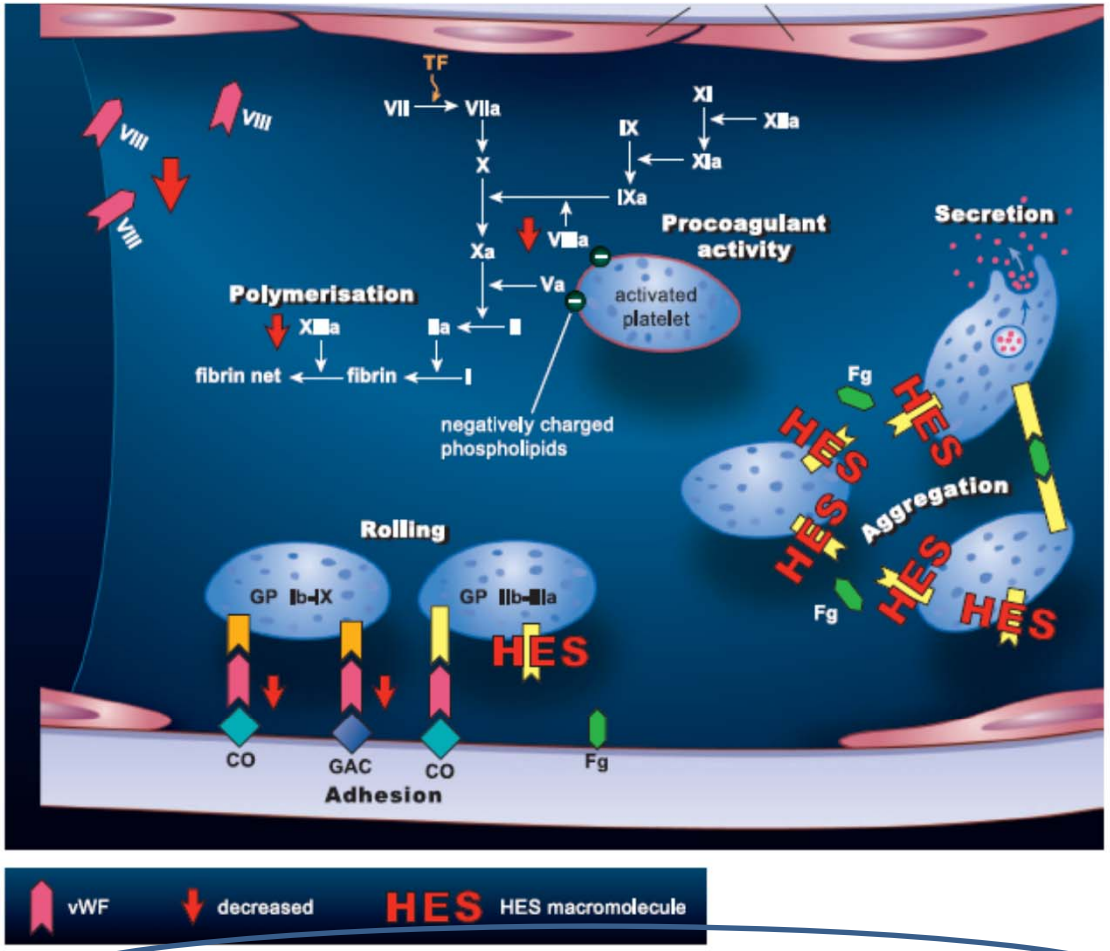


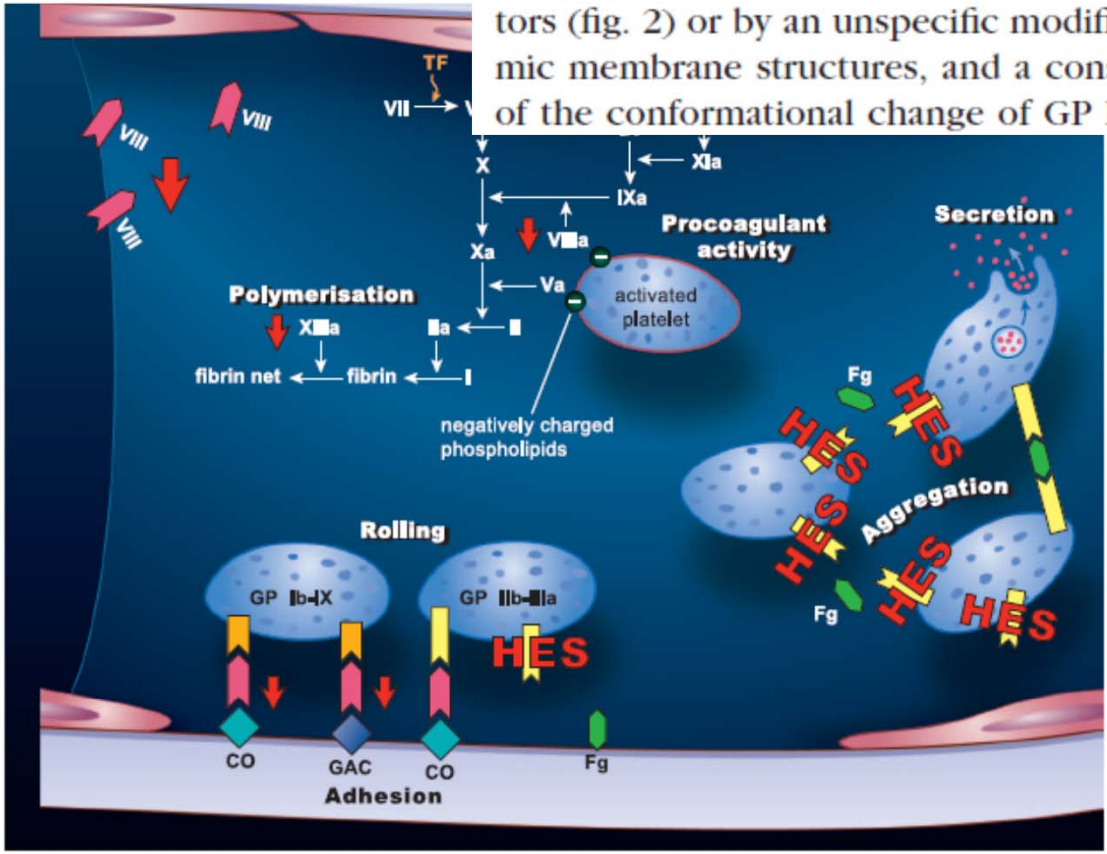
Fig. 2. Effect of hydroxyethyl starch molecules (HES) on hemostasis. Slowly degradable HES solutions decrease (*red arrows*) the plasma concentration of coagulation factor VIII and its carrier glycoprotein (GP) von Willebrand factor (*pink symbols*). Consequently, von Willebrand factor–mediated rolling and adhesion of platelets to subendothelial collagen (CO) and heparin-like glycosaminoglycans (GAC) involving platelet GP Ib–IX and GP IIb–IIIa (*light yellow symbols*) are impaired in the presence of HES.

Anesthesiology 2005; 103:654–60

Effects of Hydroxyethyl Starch Solutions on Hemostasis

*Sibylle A. Kozek-Langenecker, M.D.**

proposed by early studies. HES may inhibit platelet reactivity by blocking the access of ligands to surface receptors (fig. 2) or by an unspecific modification of cytoplasmic membrane structures, and a consecutive inhibition of the conformational change of GP IIb–IIIa. It remains



Reduced availability of activated GP IIb–IIIa by platelet surface coating of HES macromolecules (*HES*) impairs adhesion to surface-bound fibrinogen (Fg) and, most important, soluble fibrinogen (Fg) ligand binding between neighboring platelets causing platelet aggregation. Activated platelets expose negatively charged phospholipids (*black dots*) on their surface, which bind constituents of the prothrombinase (Va) and tenase complex (VIIIa; procoagulant activity). Consequently, reduced availability of the accelerator VIIIa results in diminished activation of factor X in the intrinsic coagulation pathway. HES impairs fibrin polymerization required for stable clot formation. The *in vivo* pharmacokinetic behavior of HES types, especially the *in vivo* molecular weight and HES plasma

Anesthesiology 2005; 103:654–60

Effects of Hydroxyethyl Starch Solutions on Hemostasis

*Sibylle A. Kozek-Langenecker, M.D.**

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 October 2013
EMA/640658/2013

Hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients – CMDh endorses PRAC recommendations

HES will be available in restricted patient populations

The CMDh also agreed with the PRAC recommendation that HES solutions may continue to be used in patients to treat hypovolaemia (low blood volume) caused by acute (sudden) blood loss, where treatment with alternative infusions solutions known as 'crystalloids' alone are not considered to be sufficient. In order to minimise potential risks in these patients, HES solutions should not be used for more than 24 hours and patients' kidney function should be monitored after HES administration. In addition to updating the product information, further studies should be carried out on the use of these medicines in elective surgery and trauma patients.

migliorare il trasporto di ossigeno, **si raccomanda** di impiegare le soluzioni di cristalloidi e i collodi non proteici come trattamento di prima scelta, utilizzando l'albumina al 5% come seconda scelta, quando le soluzioni di cristalloidi e i collodi non proteici siano stati già impiegati a dosaggi massimali, senza avere ottenuto una risposta clinica adeguata, e laddove i colloidi non proteici siano controindicati **[1A]**.

Si raccomanda di non utilizzare le soluzioni di amido idrossietilico per la correzione dell'ipovolemia acuta nei pazienti emorragici a causa dell'aumento del rischio di mortalità e di insufficienza renale **[1B]**.

Si raccomanda di non impiegare le soluzioni di amido idrossietilico ad alto peso molecolare allo scopo di evitare alterazioni dell'emostasi caratterizzate da ridotta funzionalità piastrinica **[1B]**.

a cura di
Stefania Vaglio, Domenico Prisco, Gianni Biancofiore, Daniela Rafanelli, PaolaAntonioli, Michele Lisanti, Lorenzo Andreani, Leonardo Basso, Claudio Velati, Giuliano Grazzini, Giancarlo Maria Liumbruno

CENTRO NAZIONALE SANGUE · SIMTI · ANMDO · PATIENT BLOOD MANAGEMENT ITALY · SIAARTI · SISET

NOTA INFORMATIVA IMPORTANTE
CONCORDATA CON L'AGENZIA EUROPEA DEI MEDICINALI (EMA) E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

Restrizione d'uso di HES
(medicinali contenenti amido idrossietilico)
Amidolite, Tetraspan,Volulyte, HAES-STERIL,Voluven, Hyperhaes, Vonten e Plasmavolume

La CE ha concluso che il rapporto beneficio-rischio per i medicinali contenenti amido idrossietilico (HES) rimane favorevole nel trattamento dell'ipovolemia causata da emorragia acuta, quando i cristalloidi da soli non sono considerati sufficienti, a condizione che siano implementate restrizioni delle indicazioni, controindicazioni, avvertenze ed altre modifiche alle informazioni contenute nel riassunto delle caratteristiche del prodotto, quali misure di minimizzazione dei rischi.

NOTA INFORMATIVA IMPORTANTE
CONCORDATA CON L'AGENZIA EUROPEA DEI MEDICINALI (EMA) E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

Restrizione d'uso di HES
(medicinali contenenti amido idrossietilico)
Amidolite, Tetraspan,Volulyte, HAES-STERIL,Voluven,
Hyperhaes, Vonten e Plasmavolume

I prodotti contenenti HES sono ora controindicati nelle seguenti condizioni:

- **Sepsi**

- **Ustioni**
- **Insufficienza renale o terapia renale sostitutiva**
- **Emorragia intracranica o cerebrale**
- **Pazienti critici (tipicamente ricoverati in Terapia Intensiva)**
- **Pazienti iperidratati, inclusi i pazienti con edema polmonare**
- **Pazienti disidratati**
- **Iperkaliemia (applicabile solo ai prodotti contenenti potassio)**
- **Grave iponatriemia o grave ipercloremia**
- **Coagulopatia grave**
- **Funzionalità epatica gravemente compromessa**
- **Insufficienza cardiaca congestizia**
- **Pazienti sottoposti a trapianto d'organo**

C'è una mancanza di dati di sicurezza consistenti a lungo termine nei pazienti sottoposti a procedure chirurgiche e nei pazienti con trauma. Il beneficio atteso del trattamento deve essere attentamente valutato in relazione all'incerto profilo di sicurezza a lungo termine, e devono essere considerati i trattamenti alternativi disponibili. Ulteriori studi saranno eseguiti con soluzioni HES in pazienti con trauma e nella chirurgia elettiva.

(Anesth Analg 2013;116:35–48

Safety of Modern Starches Used During Surgery

Philippe Van Der Linden, MD, PhD,* Michael James, MB ChB, PhD, FRCA, FCA(SA),‡
B. Weiskopf, MD¶

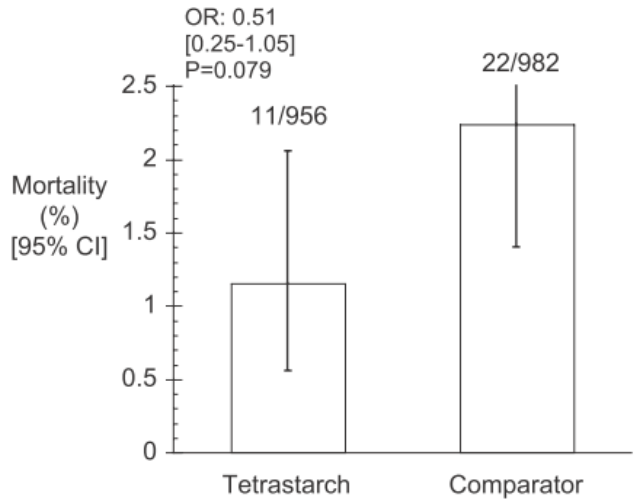

Figure 1. Mortality from all publications reporting such data. Bars are 95% confidence intervals.

ations have been used for decades to augment blood
tly regarding possible adverse outcomes when using
ially in patients with septic shock. However, the phar-
erties of HES preparations depend on their chemical
, different clinical conditions could result in differing
rations. Consequently, we assessed the safety of tetra-
starches when used during surgery, using a formal search, that yielded 59 primary full publications of studies that met a priori inclusion criteria and randomly allocated 4529 patients with 2139 patients treated with tetrastarch compared with 2390 patients treated with a comparator. There were no indications that the use of tetrastarches during surgery induces adverse renal effects as assessed by change or absolute concentrations of serum creatinine or need for renal replacement therapy (39 trials, 3389 patients), increased blood loss (38 trials, 3280 patients), allogeneic erythrocyte transfusion (20 trials, 2151 patients; odds ratio for HES transfusion 0.73 [95% confidence interval = 0.61–0.87], *P* = 0.0005), or increased mortality (odds ratio for HES mortality = 0.51 [0.24–1.05], *P* = 0.079). (Anesth Analg 2013;116:35–48)

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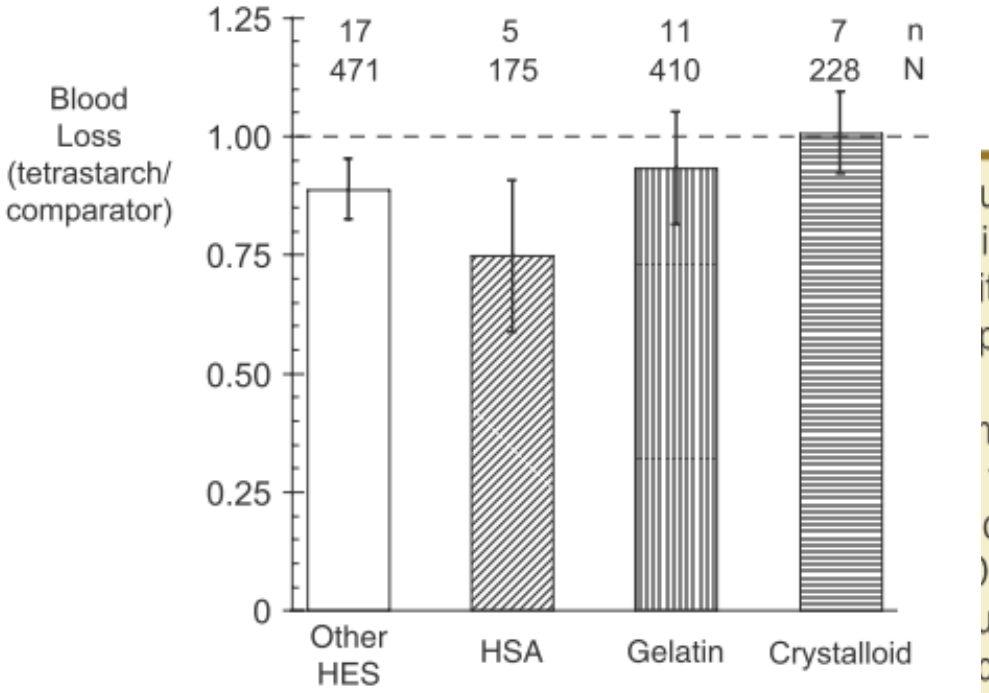
Safety of Modern Starches Used During Surgery

Philippe Van Der Linden, MD, PhD,* Michael James, MB ChB, PhD, FRCA, FCA(SA),‡
Michael Mythen, MD FRCA,‡§‖ and Richard B. Weiskopf, MD¶



used for decades to augment blood
ible adverse outcomes when using
ith septic shock. However, the phar-
parations depend on their chemical
conditions could result in differing
ntly, we assessed the safety of tetra-
that yielded 59 primary full publica-
domly allocated 4529 patients with
) patients treated with a comparator.
uring surgery induces adverse renal
of serum creatinine or need for renal
replacement therapy (39 trials, 3389 patients), increased blood loss (38 trials, 3280 patients), allogeneic erythrocyte transfusion (20 trials, 2151 patients; odds ratio for HES transfusion 0.73 [95% confidence interval = 0.61–0.87], $P = 0.0005$), or increased mortality (odds ratio for HES mortality = 0.51 [0.24–1.05], $P = 0.079$). (Anesth Analg 2013;116:35–48)

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Safety of Modern Starches Used During Surgery

Philippe Van Der Linden, MD, PhD,* Michael James, MB ChB, PhD, FRCA, FCA(SA),‡
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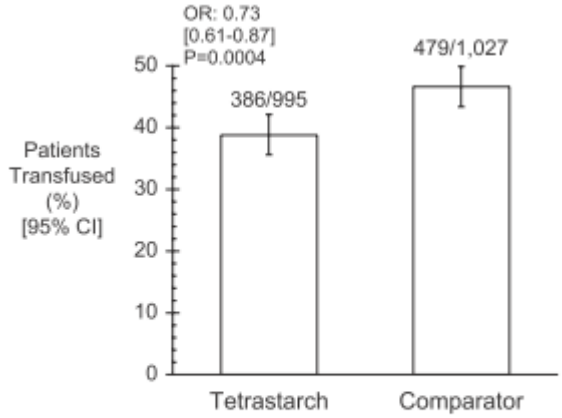

Figure 4. Fraction of patients transfused with allogeneic red cells comparing those given a tetrastarch versus all other comparators. Twenty trials reported allogeneic red cell transfusion (2151 patients); 2 reported no difference without actual data; 18 studies provided data for 2022 patients. Bars are 95% confidence intervals.

Various hydroxyethyl starch (HES) preparations have been u
volume. There has been concern recently regarding possi
HES in the intensive care setting, especially in patients wit
macokinetic and pharmacodynamic properties of HES prep
composition and source material. Thus, different clinical
effectiveness and safety for these preparations. Consequen
starches when used during surgery, using a formal search, t
tions of studies that met a priori inclusion criteria and ranc
2139 patients treated with tetrastarch compared with 2390 patients treated with a comparator.
There were no indications that the use of tetrastarches during surgery induces adverse renal effects as assessed by change or absolute concentrations of serum creatinine or need for renal replacement therapy (39 trials, 3389 patients), increased blood loss (38 trials, 3280 patients), allogeneic erythrocyte transfusion (20 trials, 2151 patients; odds ratio for HES transfusion 0.73 [95% confidence interval = 0.61–0.87], $P = 0.0005$), or increased mortality (odds ratio for HES mortality = 0.51 [0.24–1.05], $P = 0.079$). (Anesth Analg 2013;116:35–48)

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BJA

REVIEW ARTICLES

Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis

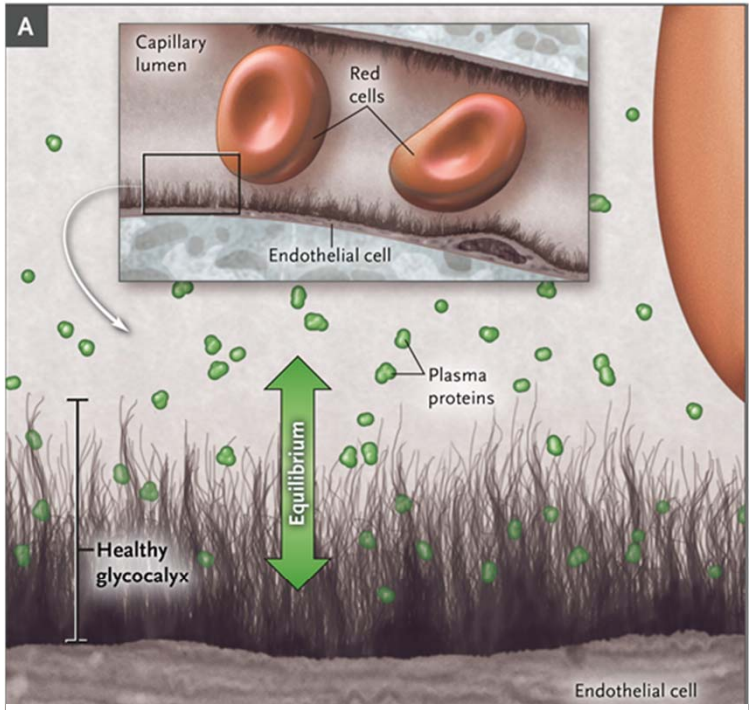
M. A. Gillies[1*], M. Habicher[2], S. Jhanji[3], M. Sander[2], M. Mythen[4], M. Hamilton[5] and R. M. Pearse[6]

Conclusion

The principal finding of this study was that there was no difference in hospital mortality, requirement for RRT, or author-defined AKI associated with perioperative use of i.v. 6% HES solutions. Although most studies were small with low event rates, there was little between-study heterogeneity and narrow confidence intervals. A very large randomized trial of 6% HES solutions would be required to demonstrate either significant benefit or harm associated with the use of these solutions in surgical patients. Given the absence of demonstrable benefit, the clear risks in critically ill patients, and the additional cost over more widely used fluids, we are unable to recommend routine clinical use of 6% HES solution in surgical patients.

Shaw AD, Kellum JA: The risk of AKI in patients treated with intravenous solutions containing hydroxyethyl starch. Clin J Am Soc Nephrol 2013; 8:497–503

clusions regarding HES difficult. The effect of fluid therapy depends deeply on an intact endothelial glycocalyx layer, which is severely compromised in patients with septicemia. Thus, the degraded glycocalyx results in immediate tissue edema, less effect of the administered fluid therapy and increased harm.[21,41]



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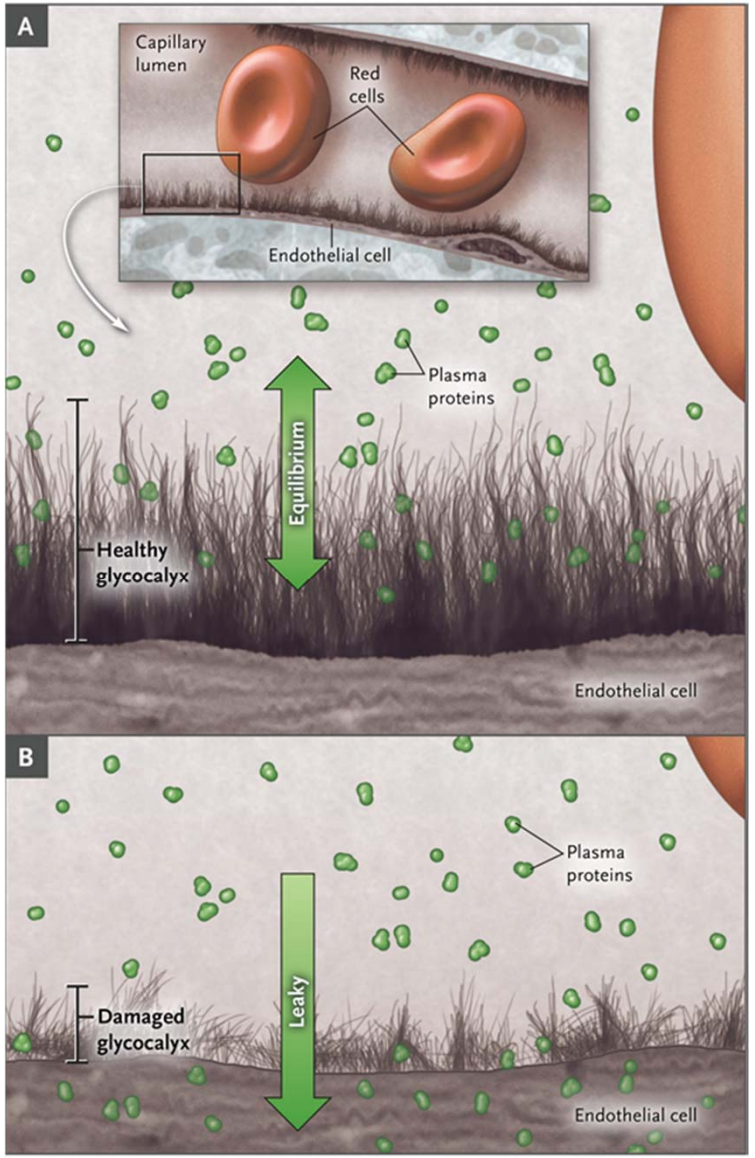
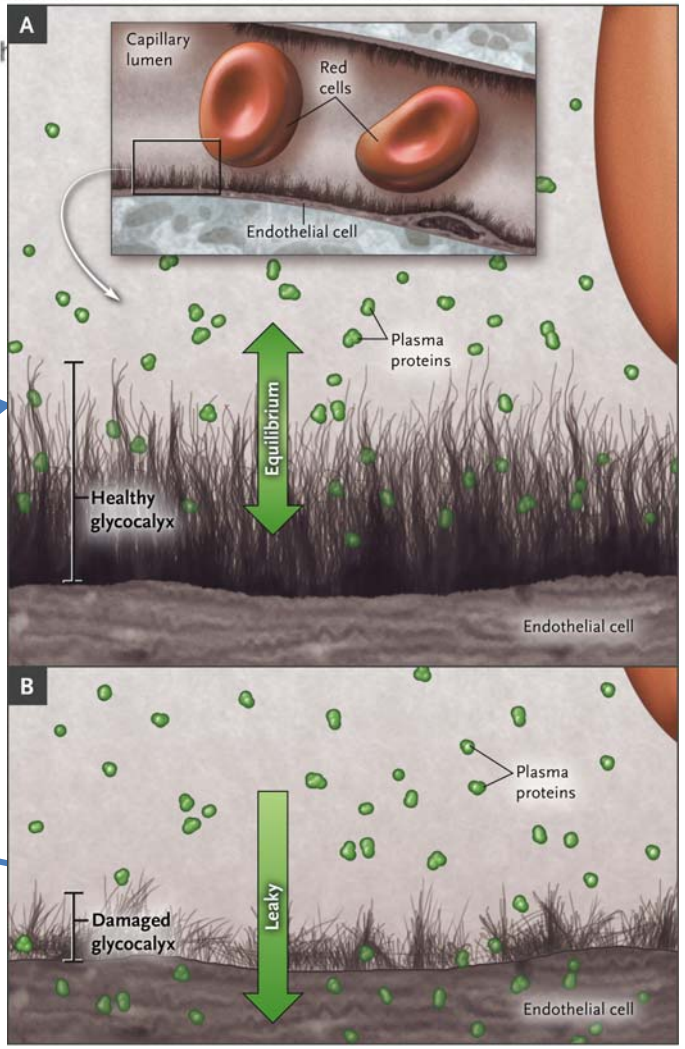


CME

Intravenous Starches: Is Suspension the Best Solution?

Karthik Raghunathan, MD, MPH,*† Timothy E. Miller, MB Ch
Andrew D. Shaw, MB, FRCA, FCCM, FFICM*†

HES. The traditional Starling model of forces governing IV fluid disposition is being revised with increasing insight into the role of the endothelial glycocalyx layer and volume context,[44,45] and physiologic appraisal suggests that traditional colloid-crystalloid distinctions may be of less importance than previously thought. The risk of using modern tetrastarch in the setting of an intact glycocalyx in the patient undergoing intravascular volume optimization early during major surgery may be potentially different than risks associated with severe sepsis where there is significant glycocalyx shedding and disruption. From a clinical standpoint: first, patients presenting for preemptive volume optimization (the population-at-risk) have a lower predicted mortality at baseline (compared with ICU patients). Assessment of mortality risks associated with use of HES during GDT would require a very large RCT (rare outcome). Second, HES during GDT is restricted to those instances where flow improves with fluid administration.[4,5] As suggested by the CRISTAL trial, safety



Update of use of hydroxyethyl starches in surgery and trauma

Richard B. Weiskopf, MD *and* **Michael F.M. James, MB, ChB, PhD**

J Trauma Acute Care Surg
Volume 78, Number 6, Supplement 1

Independent of the important methodological and interpretative flaws of two trials of HES in ICU populations (exclusively or with a substantial fraction of septic shock), there are well-established physiologic and pharmacologic principles strongly indicating that it is inappropriate to apply those data to a surgical or trauma population. In addition, there are important therapeutic differences regarding HES use in these populations (multiple doses given over several days or weeks vs. administration only for several hours). Regulatory warnings and prohibitions do not adequately address these issues. The data derived

But Is It Safe? Hydroxyethyl Starch in Perioperative Care

Steven Greenberg, MD,* and Avery Tung, MD†

March 2015 • Volume 120 • Number 3

Is HES safe for perioperative use? As no large randomized trials comparable to 6S or CHEST exist for perioperative use, a definitive answer is not possible, and existing studies regarding the perioperative nephrotoxicity of HES use are mixed.[19–22]

Clinicians might consider some general observations. First, the longevity of HES in clinical use suggests that for most patients, the magnitude of any nephrotoxic risk is likely to be small and a greater perioperative concern may be the risk of coagulopathy or anaphylactoid reaction. Second, any nephrotoxic effect is likely to be greater in patients at greater risk for perioperative renal injury. Identifying preoperative risk factors for nephrotoxicity might then assist in determining which patients, if any, might receive HES safely. Finally, existing data suggest that the magnitude of any increased overall risk attributable to HES alone (and not to factors related to HES administration such as the need for acute resuscitation) is small. Even in patients with severe sepsis[8,9] or undergoing liver transplant,[17,23] the attributable adjusted or multivariate odds ratio for renal injury or RRT is <1.4.

Fluid Overload and Surgical Outcome

Another Piece in the Jigsaw

Dileep N. Lobo, DM, FRCS

In the 16th century, Philippus Theophrastus Aureolus Bombastus von Hohenheim, better known as Paracelsus, said, "Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.'

Annals of Surgery • Volume 249, Number 2, February 2009

Recommendations for Fluid Resuscitation in Acutely Ill Patients.

Table 2. Recommendations for Fluid Resuscitation in Acutely Ill Patients.

Fluids should be administered with the same caution that is used with any intravenous drug.

Consider the type, dose, indications, contraindications, potential for toxicity, and cost.

Fluid resuscitation is a component of a complex physiological process.

Identify the fluid that is most likely to be lost and replace the fluid lost in equivalent volumes.

Consider serum sodium, osmolarity, and acid–base status when selecting a resuscitation fluid.

Consider cumulative fluid balance and actual body weight when selecting the dose of resuscitation fluid.

Consider the early use of catecholamines as concomitant treatment of shock.

Fluid requirements change over time in critically ill patients.

The cumulative dose of resuscitation and maintenance fluids is associated with interstitial edema.

Pathological edema is associated with an adverse outcome.

Oliguria is a normal response to hypovolemia and should not be used solely as a trigger or end point for fluid resuscitation, particularly in the post-resuscitation period.

The use of a fluid challenge in the post-resuscitation period (≥24 hours) is questionable.

The use of hypotonic maintenance fluids is questionable once dehydration has been corrected.

Specific considerations apply to different categories of patients.

Bleeding patients require control of hemorrhage and transfusion with red cells and blood components as indicated.

Isotonic, balanced salt solutions are a pragmatic initial resuscitation fluid for the majority of acutely ill patients.

Consider saline in patients with hypovolemia and alkalosis.

Consider albumin during the early resuscitation of patients with severe sepsis.

Saline or isotonic crystalloids are indicated in patients with traumatic brain injury.

Albumin is not indicated in patients with traumatic brain injury.

Hydroxyethyl starch is not indicated in patients with sepsis or those at risk for acute kidney injury.

The safety of other semisynthetic colloids has not been established, so the use of these solutions is not recommended.

The safety of hypertonic saline has not been established.

The appropriate type and dose of resuscitation fluid in patients with burns has not been determined.

The NEW ENGLAND JOURNAL of MEDICINE

September 2014 • Volume 119 • Number 3

Volume Therapy with Hydroxyethyl Starches: Are We Throwing the Anesthesia Baby Out with the Intensive Care Unit Bathwater?

Michael G. Irwin, MD, FHKAM, FANZCA, FRCA, DA, MB ChB,* and Tong J. Gan, MD, MHS, FRCA†