

Crystalloids and colloids

A personal view on their perioperative use

L. VEECKMAN

Since Shires' original articles (35, 36) on fluid dynamics in trauma and surgery, further studies and review articles (22) have enabled the clinician to gain a better understanding of intercompartmental fluid shifts in these patients, and hence to optimise perioperative fluid therapy.

Yet, in spite of these data, meta-analyses, national and international consensus conferences, the daily use of crystalloid or colloid fluid in surgical and critically ill patients, strongly remains a matter of personal preference and institutional tradition (37).

But can tradition and preference be upheld in an era of evidence based medicine and health economics ?

Several Cochrane meta-analyses (1, 2, 11) on the use of resuscitation fluids conclude to the absence of reduction of mortality for colloid over crystalloid resuscitation in the mixed surgical - critical care population, to the absence of clinical superiority in terms of mortality of any of the available colloid solutions in fluid resuscitation and to the potential harm in the use of albumin solutions in the critically ill.

But these meta-analyses may well have some fundamental flaws.

All three meta-analyses (and their later internal reviews) use mortality as a comparator, though it was not an end-point in many of the original studies. These studies moreover span a period of over 25 years, with a large part of the colloid studies on albumin, and some of the crystalloid studies on hypertonic saline. And as their titles indicate, the target populations of the different meta-analyses differ, and should not be confounded. The original and best known 1998 crystalloid-colloid meta-analysis published in the British Medical Journal (34), produced an overall mortality odds ratio of 1,29 favouring crystalloids, reporting 4% increased mortality for colloid use. But closer inspection of these data reveals a major difference between patient subpopulations : colloid usage in the trauma patients had an odds ratio for mortality

of 1,24. Colloid usage in surgical patients however – and these are the patients we anaesthetists most often deal with - had an odds ratio of 0,55, clearly favouring the use of colloids. Things get even more confounding. When linking these data to the results published in further Cochrane analyses major heterogeneity and internal conflicts arise. In the 2000 review on crystalloids and colloids, gelatin based solutions definitely score better than crystalloids and far better than any of the other available colloids (odds ratio gelatin-crystalloids 0,55 – odds ratio HES-crystalloids 1,16). Yet the conclusions from the 2003 colloid-colloid analysis shows no superiority of one colloid over another ?? Even albumin does well in this review !!

With the Cochrane meta-analyses, one of the “prime tools of evidence based medicine” hardly helpful in clearing the fog over the crystalloid-colloid controversy, I feel somewhat left out in the cold. Data presented in the next section hence reflect my personal opinion. Discussion will focus both on the individual characteristics of available resuscitation fluids and on their usage in specific population subsets.

Properties of the “ideal plasma substitute” (10)

Distributed in intravascular compartment only
Readily available
Long shelf half-life
Inexpensive
No special storage or infusion requirements
No special limitations on volume that can be infused
No interference with blood grouping or cross-matching
Acceptable to all patients & no religious objections to its use.
Iso-oncotic with plasma
Isotonic
Low viscosity
Contamination easily detected
Half-life should be 6-12 hours
Should be metabolised or excreted, not stored in body.

Dr. L. VEECKMAN, Anaesth. Dept., University Hosp. UZ KU Leuven, Herestraat 49, 3000 Leuven.

No interference with organ function, even with repeated administration
 Non-pyrogenic, non-allergenic, non-antigenic
 No interference with haemostasis or coagulation
 Not cause agglutination or damage to blood cells
 No effect on immune function including resistance to infection
 No effect on haematopoiesis
 Not cause acid-base disorders
 Not cause or promote infection (bacterial, viral, protozoal, prion disease, ...)

CRYSTALLOIDS – ISOTONIC

Mainstay of many US resuscitation protocols.
 Allegedly the cheapest resuscitation fluid.

Doing extremely well in the Cochrane analysis : but only in burns and trauma patients. Not in the average surgical patient (odds ratio 0,55 vs. the combined odds ratio of 1,29). Major capillary leak in burn and critically ill septic patients allow for colloid (especially the smaller sized albumin – some evidence of capillary-leak plugging with the MMW and LMW hydroxyethyl starches) to leak into the interstitial space. Better volume effect and more rapid restoration of haemodynamic parameters (blood pressure, frequency, cardiac output) with colloid administration may conflict with current insights in fluid resuscitation of the bleeding trauma patient (28, 33).

But crystalloids are severely hampered by a limited intravascular persistence : after intravenous administration of 1 liter sodium chloride or lactated Ringer's solution, at best 33% is retained in the intravascular space. These rates may be slightly better when starting off with an hypovolemic patient (14) but increase dramatically in a model of sustained normovolemic haemodilution (12) (the surgical model). This need for repetitive administration clearly reduces the cost-effectiveness of crystalloid administration : in a 2000 article J. Boldt (9) performed a cost analysis of different volume replacement strategies in anaesthesia, and found very little difference.

And the limited intravascular persistence also potentially results in an excessive distribution of fluid into the interstitial space. Older literature data on the impact of excessive crystalloid administration on interstitial oedema, and even on the generation of postoperative pulmonary oedema in non-pneumectomy patients, are controversial. Major dynamic reserves in lymph flow and oxygen extraction capacity of several organs partly explain these controversial results. Yet, more specific evaluation of tissular function during various resuscitation protocols has been evaluated in several recent

studies. The value of recently published data on the effects of the various resuscitation protocols on tissular paO_2 (19, 20, 38) and on peri-operative morbidity and mortality, isn't fully elucidated yet. Both studies however show a tendency for colloids to be the better resuscitation fluids : better volume restoration and reduced tissular oedema are thought to play an important role in these findings.

By contrast, theoretical deleterious effects of hypotonic solutions on brain oedema are well demonstrated for (large volumes of) glucose containing solutions. Slightly hypotonic solution such as Lactated Ringer's solution may be a cause of brain oedema with the infusion of major doses (> 50 ml/kg). The necessity to substitute lactated Ringer's solution by non-lactated crystalloids (e.g. as Plasmalyte®) in the setting of splanchnic and hence hepatic hypoperfusion during shock resuscitation is still somewhat controversial. The increased cost of these solutions and their short intravascular persistence narrows the difference with the colloid solutions. The physiological impact of the hyperchloremic acidosis associated with the administration of Normal Saline (> 30 ml/kg) and with the NaCl dissolved colloids is unclear.

CRYSTALLOIDS – HYPERTONIC

Administration of hypertonic saline, hypertonic saline in dextran or hypertonic saline in hydroxyethyl starch results in a net increase in oxygen delivery, not only by volume expansion, but also by an intrinsic inotropic and chronotropic effect. With an average administration of 4 ml/kg of NaCl 7,2 or 7,5%, volume expansive effects attained a maximum at 120% and sustained a plateau at over 60% for a period well over 150 minutes. This preload increase is accompanied by an afterload reduction through an improved microcirculation (endothelial shrinkage, improved forward flow), and – in an euvoletic animal model – by a direct positive inotropic and chronotropic effect. Hypovolemia, both in animals and humans, augments these direct cardiac effects, whereas anaesthesia – at least in humans – blunts the inotropic effect.

Clinical trials with hypertonic solutions in aortic aneurysm surgery, coronary artery bypass surgery, neurosurgery and trauma care resulted in a reduced fluid volume requirement, better tissue perfusion and reduced postoperative bleeding. But there are some caveats : especially in patients with

a limited left ventricular function, the use of a fixed dose of hypertonic solutions should be dissuaded from (hypotension and an increased incidence of left ventricular failure). Dose determination by physiological endpoints as suggested by Ellinger and colleagues (16) and tempered rates of administration should be advocated in these, if not all patients. The exact impact of the volume expansion by the administration of hypertonic solutions on pulmonary function and lung water are unclear, but appear clinically non significant. In a similar way, the post-administration hemodilution and dilution of clotting factors appears to remain without clinical impact. In fact, outcome in trauma patients appears unaffected by the administration of hypertonic solutions, in spite of the theoretical deleterious effects of hypervolemia and a theoretically impaired coagulation system. And finally, the sporadic occurrence of an undercontrolled hypernatremia (most studies use sodium levels > 155-160 mEq/l and or plasma osmolality > 320-330 mOsm/kg as cut-off values) was not associated with central pontine myelolysis or any other untoward side-effect. In almost every case, sodium levels returned to baseline values over the next 24 hours.

But in spite of the theoretical and some of the clinical advantages mentioned before, major outcome studies (45) in trauma patients show a minimal, non statistically significant improvement with the use of hypertonic solutions over traditional isotonic resuscitation protocols. Hypertonic saline resuscitation thus remains the instrument of the enthusiastic proponent, and of the burn-care centers.

DEXTRAN BASED COLLOIDS

Due to their high allergenic properties, the dextran based colloids (both 40.000 kD and 70.000 kD solutions) are no longer used for fluid resuscitation. As result of their profound effect on haemeostasis, their use for their rheological properties has also somewhat waned.

ALBUMIN COLLOIDS

This naturally occurring plasma protein has long been judged the "gold standard" of fluid resuscitation.

Absence of risk for disease transmission resulting from its manufacturing process, absence

of volume restrictions, low allergenicity, absence of significant nephrotoxicity and absence of intrinsic coagulopathy however is at a price : albumin solutions are 50 times more expensive than crystalloids and 6 times more expensive than starch-based colloids.

So they must be better.

And their kinetics aren't all that spectacular : isotonic 4% solutions are mainly used during volume resuscitation therapy, but have a volume substitution effect ceiling at 80% of their infused volume. Hyperoncotic 20% solutions are mainly used for correction of hypo-albuminemia and low oncotic states in critically ill, and have a volume expansive effect of 300-400%. Intravascular persistence is limited to 6-8 hours, and their commercial availability in glass containers limits rapid administration. Attempts at pressurised administration may even be extremely hazardous.

And they're killed off by the 2000 Cochrane meta-analysis (1), showing an increased mortality with administration of albumin (both types) in critically ill patients (odds ratio 1,52). But these data are challenged. In a 2001 similarly conducted meta-analysis, Wilkes (47) found no difference in mortality between groups. Similar data emerge from earlier studies by Foley, Stockwell and Boldt, and Grundmann who were unable to demonstrate any beneficial effect on mortality and hospital stay with albumin administration for hypo-albuminemia, fluid resuscitation in critical illness or restoration of colloid osmotic pressure respectively.

But, JL Vincent's (43) recent study opens a small door for the intuitive albumin user and its manufacturer. Although the study also was unable to demonstrate a clear benefit from albumin administration to correct hypo-albuminemia in critical-illness, they conclude that the clinician no longer should withhold from albumin administration, if judged clinically appropriate. Henceforth to conclude that perioperative prophylactic administration of albumin solutions to patients at risk may be of benefit, does need well controlled further investigation.

Data for "cosmetic" administration of hyperoncotic albumin solutions to treat oedema states of the critically ill (often in association with diuretics) are controversial at the best. Although there is a net effect on migration of fluid into the vascular space in healthy individuals, this effect is less marked in critically ill patients, where leaky capillary membranes may even result in an accentuation of the interstitial edema.

GELATIN BASED COLLOIDS

In spite of the introduction of gelatin based plasma substitutes, hard literature data are scarce. Its relative age (first used in 1915, commercially available since 1950) and absence of the commercial market in the United States for the last decades, may partially explain this paucity.

At best they are volume substitutes, with a volume effect of approximately 80% (3,9,30) in most studies, although 100% volume replacement has been noted in hypovolemic patients. Half-life is limited to 2-3 hours, essentially by renal clearance. This limited half-life and slightly reduced volume expansive effect results in a 25-30% increased volume usage over hydroxyethyl starch solutions, and a virtual abolishing of cost benefit (9).

Main drawback of the gelatin based colloids is their increased risk for anaphylactic or anaphylactoid reactions (26, 29). In the 1994 study on allergic reactions in France, Laxenaire reported a 6 fold higher incidence of allergic reactions to gelatin solutions compared to the hydroxyethyl starches. In the 2003 study virtually all allergic reactions to colloid solutions were attributable to gelatin.

A second issue is the potential for gelatin based solutions to interfere with coagulation (13, 15, 27), as evaluated by thrombelastography or laboratory evaluation of coagulation. Interaction with fibronectin, decreased levels of von Willebrand factor and potential interference with fibrinogen cross-anchoring have been demonstrated: clinical effects on blood loss and transfusion requirements however appear to be minimal (13, 30). Minimal differences in coagulation effects to the disadvantage of the urea-linked (Haemaccel®) gelatins have been reported: in a 1997 study using succinylated gelatin, Mortier (31) was unable to reproduce the TEG effects, even after an in vitro 50% haemodilution.

And, although company certified to be prion free, public sensitisation about transfusion related transmission of infectious disease led several medical communities to reluctantly use this beef collagen derivative. Its effect as contaminant of the biuret assay for albumin most likely is marginal.

STARCH BASED COLLOIDS

Starch based colloid solutions were first introduced in the mid sixties (40), and have been used commercially for some 30 years now. When evaluating the effects and side-effects of the hydrox-

ethyl starch solutions, the presence of major differences between commercially available subtypes should fully be appreciated. Not all HES are equal. Discussion however will be limited to hydroxyethyl starch solutions that have been or are currently available on the Belgian market.

The first generation hydroxyethyl starch solutions were mainly aimed at volume expansion and intravascular persistence (hetastarch – HES 450/0,7 – Plasmasteril®) through high molecular weight and optimal chemical substitution to withstand biological degradation by α -amylase. These HMW hydroxyethyl starches however had several major drawbacks.

They interfered significantly with several initial steps of normal coagulation, especially by reducing von Willebrand and ristocetin cofactor, thus reducing platelet adhesiveness and aggregation. In contrast to the majority of gelatin related studies, several studies on the clinical effects of high molecular weight hydroxyethyl starch solutions do describe significant increases in peri-operative blood loss and transfusion requirements.

A further, potentially deleterious effect of the high MW hydroxyethyl starches is their potential decrease perioperative renal function, as well in patients with pre-existing renal function impairment, as in patients at risk for renal dysfunction (donor exposed transplant kidneys, septic patients). Renal dysfunction however could not be induced by the mere administration of HMW HES in healthy well hydrated individuals (44) – even if elderly (25). In the exposed-donor renal transplant group moreover, the presence of “osmotic nephrosis-like” lesions appeared to have no impact on recovery of renal function at 3 or 6 months post-transplant.

Binding of amylase to the hydroxyethyl starch molecules almost invariably increases serum amy-lasemia, making biochemical diagnosis of acute pancreatitis difficult. Biodegradation of the hydroxyethyl starch molecules however stops at about 50 kD polymers (renal elimination threshold), without metabolism continuing to the point of formation of glucose or hydroxyethylglucose (and resultant hyperglycemia).

Slow elimination, tissular deposition and macrophage uptake result in delayed pruritus and subclinical interference with immunocompetence. As a result of these side-effects, maximal dose guidelines were issued at 20 ml/kg/day; which in itself limits the clinical use of HMW starches.

Smaller, but still quite heavily substituted hydroxyethyl starches (200/0,62 – hexastarch –

Elo-HAES®) retain some of the undesired side-effects of the HMW hydroxyethyl starches. Both the heta- and hexastarches are hardly used in Belgium.

Smaller and less substituted hydroxyethyl starches (HES 200/0,5 or pentastarch – HAES-Steril® and especially HES 130/0,4 or tetrastarch – Voluven®) appear to have a better safety profile. They share a virtual 100% volume substitution effect, which is maintained for approximately 6 hours. Renal elimination is more complete than with the “older” hydroxyethyl starch solutions, resulting in a reduced incidence of pruritus. Maximal daily doses are increased to 33 and 50 ml/kg/day for penta- and tetrastarch solutions respectively. Moreover, the incidence of hyperoncotic renal dysfunction (6, 7), and the effects on coagulation are less pronounced than with the HMW hydroxyethyl starches, the latter mainly occurring in in vitro dilutional studies. The general recommendations from BOLDT (8) in a 2002 review on renal effects of hydroxyethyl starch solutions cautioning on the use of low molecular weight HES in patients with established renal function impairment (plasma creatinine > 3 mg/dl). Whether this recommendation should henceforth be restricted to the HES 200/0,5 solutions after reading the Jungheinrich (23) data on the administration of HES 130/0,4 in patients with severe renal failure (Cl_{creat} 30-15 ml/min), is not fully clear in view of the limited amount HES 130/0,4 administered (500 ml).

With some of the data of this previous section in mind, we'll take a 180 degree turn, and look at literature data on colloids and crystalloids in specific patient subpopulations.

CRYSTALLOIDS AND COLLOIDS IN : PAEDIATRICS

Because of the poor insurability of children in clinical studies, data on crystalloid and colloid resuscitation in children are scarce. Preferential use of albumin colloid and/or plasma in pump prime emerged from a questionnaire in the united states, where 85% of the 1995 respondents used albumin vs. 34% in 1989.

CRYSTALLOIDS AND COLLOIDS IN : NEURAXIAL BLOCKS INCL. OBSTETRICS

Although literature data support the superior effectiveness of colloids over crystalloids in the

prevention of post-spinal hypotension in virtually all examined populations (including geriatric and obstetric groups - populations most at risk) most studies conclude to the limited clinical value of the results, as severe hypotension was never fully excluded (therapeutic efficacy 80%) and – in obstetrics – the occurrence of (vasopressor corrected) maternal hypotension did not influence foetal outcome. Although colloid – or mixed colloid crystalloid – volume pretreatment is beneficiary, it should not be a reason to delay the institution of a neuraxial blockade in a semi-urgent clinical situation (eg. Caesarean section) (46).

CRYSTALLOIDS AND COLLOIDS IN : NEUROSURGERY

Hypertonic solutions may be of benefit here, although their haemodynamic effects are rather shortlived, and absence of improved outcome widespread use somewhat limits its clinical breakthrough.

Hyperosmolar colloids (HES 200/0,5 10%) like hypertonic crystalloids result in volume-expansion upon administration, thus more adequately restoring the cerebral perfusion pressure, without migration across the blood brain barrier. In our institution these colloids are used as primary resuscitation fluid on the trauma scene.

Hydroxyethylstarch 130/0,4 also shows some promising results in neurosurgery. In a 2003 study on the use of HES 130/0,4 in neurotrauma, NEFF (33) concluded to superior effects of HES 130/0,4 over HES 200/0,5 (with additional use of albumin when HES 200/0,5 volume limits were reached) in terms of incidence and extent of intracranial hypertensive episodes. However, these beneficial effects did not reflect in a decreased mortality or in an improved Glasgow outcome score.

CRYSTALLOIDS AND COLLOIDS IN : THORACIC SURGERY

Although patients with thoracic surgery are renown for massive perioperative volume shifts, and the relationship between post-pneumonectomy pulmonary oedema and overhydration is well established, data about effects of perioperative volume substitution therapy in thoracic surgery are scarce. Data on colloid osmotic pressure drops (plasmapheresis) in healthy animals tend to favour colloid administration, and all show a dramatic reserve of the pulmonary lymph flow to stabilise

extravascular lung water. This beneficiary effect of colloids however disappears after microembolism induced pulmonary lesions: vascular pressure becomes dominant over colloid osmotic pressure (Starling equation). Outcome studies of ARDS patients with continued fluid requirements post resuscitation indeed show an increased mortality and prolonged hospital stay over patients resuscitated with crystalloid regimens. JL Vincent in a 1991 symposium report (42) on crystalloids and colloids points out the theoretically more pronounced impact of altered pulmonary capillary pressure with colloid resuscitation, which may offset its beneficiary effects on COP, especially in settings of inadequate membrane stability.

Human outcome studies however comparing crystalloid and colloid resuscitation schemes in thoracic surgery however are not readily available.

CRYSTALLOIDS AND COLLOIDS IN : CARDIAC SURGERY

Whereas a study by Boldt indicates an increased morbidity with the use of crystalloids for pre-bypass acute plasmapheresis, a brief literature review on the use of the various colloids in adult cardiac surgery reveals no major advantages for any the contemporary solutions. HES 130/0,4 and albumin appear to be devoid of the interference with normal coagulation that can be observed with the administration of high doses gelatin solutions and HES 450 and HES 200 solutions. High dosed gelatin moreover appears to reduce the aprotinin effect on perioperative blood loss.

Although producing improved microcirculatory conditions both prior to after extracorporeal bypas, while best maintaining haemodynamic stability, hypertonic colloid solutions have a time-limited clinical efficacy (ca. 120 minutes) and should

be used cautiously in patients with a limited ventricular function (hypotension and tachycardia).

CONCLUSION

In conclusion, definite guidelines on the preferential use of crystalloids or colloids cannot be put forward at this time. Most likely, as already indicated by Shires in his cornerstone article on fluid resuscitation in 1961, and restated by HILMANN (22) and Haljamaä, as both types of fluids replenish a different part of the extracellular compartment, crystalloid AND colloid resuscitation most likely will be the way to go in the next decades.

It is my belief that in spite of its economical attractiveness, an exclusive crystalloid resuscitation, which mainly repletes the interstitial space, may not be the state of the art in large volume resuscitations. With reduced volume resuscitations and as part of a balanced administration of plasma substitutes, crystalloid solutions however can be used safely.

The universal use of albumin solutions - especially with regard to cost-effectiveness - offers no benefit. However, if volume limits for further colloid administration are reached, or if a more lasting volume effect is desired, the use of albumin should no longer be condemned as obsolete.

Although I tend to a personal preference for the use of the new HES 130/0,4 for colloid resuscitation, I have to admit that at the moment literature data are just reaching us, and that some study conclusions may not be fully conclusive.

The need for further study tends to be universal problem in today's quest for evidence based data. Quoting a quote () from Boldt's review: so little done, so much to do.

Comparative data for crystalloids and colloids

	Hartmann 1000	Plasmalyte A	Albumin 4%	Albumin 20%
Unit price	2,0 €	3,36 €	44,72 €	63,06 €
Type	Crystalloid	Crystalloid	Albumin	Albumin
Average MW (kD)	-	-	85000	69000
Intravascular t ?	-	-	6-8	6-8
COP	-	-	20	80
Osmolariteit	273 mosm/l	295 mosm/l	250-350 mosm/l	
Unit volume	500 & 1000 ml	500 & 1000 ml	250 & 400 ml	100 ml
Volume effect (plateau)	18-33%	18-33%	85-90%	300-400%

Electrolytes	Na 130 mEq/l Cl 109 mEq/l K 4,0 mEq/l Ca 2,7 mEq/l Lactate 28 mEq/l	Na 140 mEq/l Cl 98 mEq/l K 5,0 mEq/l Mg 3,0 mEq/l Acetate 27 mEq/l Gluconate 23 mEq/l	Polyionic	Sodium poor
Maximal daily dose	–	–	–	–
Allergenic	–	–	0,129%	0,129%
Intrinsic effect on coagulation tests	–	–	–	–
Renal function	–	–	–	Extremely rare

	Rheomacrodex	Geloplasma 3%	Gelofusine 4%	Haemaccel 3,5%
Unit price	11,30 €	4,21 €	4,18 €	4,83
Type	Dextran	Succinylated Gelatin	Succinylated Gelatin	Urea-linked modified fluid gelatin
Average MW (kD)	40000	35000	30000	30000
Intravascular t ?	8 h	2-3 h	2-3 h	2-3 h
COP	Nd.	29	34-42	26-29
Osmolariteit	280-315	320	340	300
Unit volume	500 ml	500 ml	500 ml	500 ml
Volume effect (plateau)	120%	80%	90%	70%
Electrolytes	Na 154 mEq/l Cl 154 mEq/l	K 5 meq/l Lactate 30 meq/l	Na 154 Cl 120	Na 145 K 5,1 Ca 6,25 Cl 125
Maximal daily dose	–	–	–	–
Allergenic	0,273%	0,345%Na 154 mEq/l Cl 154 mEq/l	0,345%	0,345%
Intrinsic effect on coagulation tests	Marked	Possible	Possible	Possible
Renal function	Rare	–	–	-

	Plasmasteril 6%	HAES Steril 6%	HAES Steril 6%	Voluven 6%
Unit price	Not available	9,20 €	9,20 €	9,20 €
Type	Hetastarch	Pentastarch	Pentastarch	Tetrastarch
Average MW (kD)	450 kD	200 kD	200 kD	130000
Substitution ratio	0,7	0,5	0,5	0,4
C2 :C6 ratio	65%	45%	45%	10%
Intravascular t ?	9-12 h	4-8	4-8	4-6
COP	30	36	36	36
Osmolariteit	310-320	308 mosm/l	308 mosm/l	308 mosm/l
Unit volume	500 ml	500 ml	500 ml	500 ml
Volume effect (plateau)	100-130%	100%	100%	100%
Electrolytes	Na 154 Cl 154	Na 154 mEq/l Cl 154 mEq/l	Na 154 mEq/l Cl 154 mEq/l	Na 154 mEq/l Cl 154 mEq/l
Maximal daily dose	20 ml/kg	30 ml/kg	30 ml/kg	50 ml/kg
Allergenic	0,059%	0,058%	0,058%	0,058%
Intrinsic effect on coagulation tests	Pronounced	Intermediate	Intermediate	Minimal
Renal function	Pronounced	Possible	Possible	Rare ? ? ?

For maximal daily doses (-) : current data for reset hemoglobin triggers make coagulation parameters the more likely limit for administration of large doses of plasma substitutes.

References

1. Alderson P, Bunn F, *et al.*, *Human albumin solutions for resuscitation and volume expansion in critically ill patients*, COCHRANE DATABASE SYST. REV., 2002.
2. Alderson P, Schierhout G., *et al.*, *Colloids versus crystalloids for fluid resuscitation in critically ill patients*, COCHRANE DATABASE SYST. REV., 2002.
3. Beyer R., Harmening U., Rittmeyer O., Zielmann S., Mielck F., Kazmaier S., Kettler D., *Use of modified fluid gelatin and hydroxyethyl starch 200/0,5 for colloidal fluid replacement in major orthopaedic surgery*, BJA, **78**, 44-50, 1997.
4. Boldt J., *Volume replacement in the surgical patient : does the type of solution make a difference. Review article*, BJA, **84** (6), 783, 2000.
5. Boldt J., Heesen M., Müller M., Pabsdorf M., Hempelmann G., *The effects of albumin versus hydroxyethyl starch solution on cardiorespiratory and circulatory variables in critically ill patients*, ANESTH. ANALG., **83**, 254-261, 1996.
6. Boldt J., *Hydroxyethyl starch as a risk factor for acute renal failure : is a change of practice indicated ?*, DRUG SAF., **25** (12), 837-46, 2002.
7. Boldt J., Brenner T., Lehmann A., Lang J., Kumle B., Werling C., *Influence of two different volume replacement regimens on renal function in elderly patients undergoing cardiac surgery : comparison of a new starch preparation with gelatin*, INTENSIVE CARE MED., **29** (5), 763-9, 2003 May.
8. Boldt J., Priebe H. J., *Medical intelligence : Intravascular volume replacement therapy with synthetic colloids : is there an influence on renal function ?*, ANES. ANALG., **96** (2), 376-382, 2003.
9. Boldt J., *Cost analysis of different volume replacement strategies in anesthesia*, INFUS. THER. AND TRANSFUS. MED., **27**, 38-43, 2000.
10. Brandis K. www.qldanaesthesia.com/fluidbook.
11. Bunn F, Alderson P., *Colloid solutions for fluid resuscitation*, COCHRANE DATABASE SYST REV. (1) CD001319, 2003.
12. Cervera A. L., Moss G., *Crystalloid distribution following hemorrhage and hemodilution : mathematical model and prediction of optimal volumes for equilibration at normovolemia*, J. TRAUMA, 506-520, 1974.
13. de Jonge E., Levi M., Berends F., van der Ende A. E., ten Cate J. W., Stoutenbeek C. P., *Impaired haemostasis by intravenous administration of a gelatin-based plasma expander in human subjects*, THROM. HAEMOST., **79**, 286-90, 1998.
14. Drubin D., Hahn R. G., *Volume kinetics of Ringer's solution in hypovolemic volunteers*, ANESTHESIOLOGY, **90**, 81-91, 1999.
15. Egli G. A., Zollinger A., Seifert B., Popovic D., Pasch T., Spahn D. R., *Effect of progressive haemodilution with hydroxyethyl starch (200/0,5), gelatin and albumin on blood coagulation*, BJA, **78**, 684-689, 1997.
16. Ellinger K., Fahnle M., Schroth M., Albrecht D. M., *Optimal preoperative titrated dosage hypertonic-hyperoncotic solutions in cardiac risk patients*, SHOCK, **3**, 167-172, 1995.
17. Feldman Z., Zachari S., *Brain edema and neurological status with rapid infusion of lactated Ringer's or 5% dextrose solution following head trauma*, J. NEUROSURG., **83** (6), 1060-1066, 1995 Dec.
18. Foley E. F., Borlase B. C., Dzik W. H., Bistran B. R., Benotti P. N., *Albumin supplementation in the critically ill*, ARCH. SURG., **125**, 739-742, 1990.
19. Friedman Z., Berkenstadt H., Preisman S., Perel A., *A comparison of Lactated Ringer's solution to HES 6% in a model of severe shock and continuous bleeding in dogs*, ANES. ANALG., **96** (3), 39-45, 2003.
20. Funk W., Baldinger V., *Microcirculatory perfusion during volume therapy. A comparative study using crystalloid or colloid in awake animals*, ANESTHESIOLOGY, **82**, 975-982, 1995.
21. Grundmann R., Heistermann S., *Postoperative albumin infusion based on colloid osmotic pressure*, ARCH. SURG., **120**, 911-915, 1985.
22. Hillman K., Bishop G., Bristow P., *The crystalloid versus colloid controversy : Present status*, BALLIÈRE'S CLINICAL ANESTHESIOLOGY, **11**, 1, 1997.
23. Holte K., Sharrock N. E., Kehlet H., *Pathophysiology and clinical implications of perioperative fluid excess*, BJA, **89** (4) : 622-632, 2002.
24. Jungheinrich C., Scharpf R., Wargenau M., Bepperling F., Baron J. F., *The pharmacokinetics and tolerability of an intravenous infusion of hydroxyethylstarch 130/0,4 (6%, 500 ml) in mild-to-severe renal impairment*, ANESTH. ANALG., **95** (3) : 544-51, 2002 Sept.
25. Kreimeier U., Prueckner S., Peter K., *Permissive hypotension Schweiz*, MED. WOCHENSCHR., **130**, 1516-1524, 2000.
26. Kunle B., Boldt J., Piper S., Schmidt C., Suttner S., Salopek S., *The influence of different intravascular volume replacement regimens on renal function in elderly*, ANESTH. ANALG., **89** (5) : 1124-30, 1999 Nov.
27. Laxenaire M. C., Charpentier C., Feldman L., *Anaphylactoid reactions to colloid plasma substitutes : Incidence, risk factors, mechanisms : a French multicenter prospective study*, ANN. FR. ANESTH. REANIM., **13**, 301-10, 1994.
28. Mardell S. N., Saunders F., Ollerenshaw I., Edwards C., Baddeley D. T., *Reduced quality of in-vitro clot formation with gelatin based substitutes*, LANCET, **347**, 825, 1996.
29. McIlroy D. R., Karasch E. D., *Acute intravascular volume expansion with rapidly administered crystalloid or colloid in the setting of moderate hypovolemia*, Anes. Analg., **96** (6), 1572-1577, 2003.
30. Mertes P. M., Laxenaire M. C., Alla F., *et al.*, *Anaphylactoid and anaphylactoid reactions occurring during anesthesia in France 1999-2000*, ANESTHESIOLOGY, **99** (3), 536-45, 2003.
31. Mortelmans Y. J., Vermaut G., Verbruggen A. M., Arnout J. M., Vermylen J., Van Aken H., Mortelmans L. A., *Effects of 6% hydroxyethyl starch and 3% modified fluid gelatin on intravascular volume and coagulation during intraoperative hemodilution*, ANESTH. ANALG., **81** (6), 1235-42, 1995 Dec.
32. Mortier E., Ongenaë M., De Baerdemaeker L., Herregods L., Den Blauwen N., Van Aken J., Rolly G., *In vitro evaluation of the effect of profound haemodilution with hydroxyethyl starch (200/0,5) 6%, modified fluid gelatin 4% and dextran 40 10% on coagulation profile measured by thromboelastography*, ANAESTHESIA, **52**, 1061-1064, 1997.
33. Neff T. A., Doelberg M., Jungheinrich C., Sauerland A., Spahn D. R., Stocker R., *Repetitive large-dose infusion of the novel HES 130/0,4 in patients with severe head injury*, ANES. ANALG., **96** (5), 1453-9, 2003.
34. Rhodes Cecil.
35. Roberts I., Evans P., Bunn F., Kwan I., Crowhurst E., *Is the normalisation of blood pressure in bleeding trauma patients harmful ?*, VIEWPOINT LANCET, **357**, 385-388, 2001.
36. Schierhout G., Roberts I., *Fluid resuscitation with colloid or crystalloid solutions in critically ill patients : a systematic review of randomised trials*, BMJ, **316** (3) : 961-964, 1998.
37. Shires G. T., Brown F. T., Canizaro P. C., Sommerville N., *Distributional changes in extracellular fluid during acute hemorrhagic shock*, SURG. FORUM, **11**, 115, 1960.
38. Shires G. T., Williams J., Brown F., *Acute changes in extracellular fluids associated with major surgical procedures*, ANN. SURG., **154**, 803, 1961.

39. Sirchia G., Giovanetti A. M., McClelland D. B. L., Fracchia G. N., *Safe and Good use of blood in surgery (SANGUIS). Use of blood and artificial colloids in 43 European hospitals*, European Commission, Brussels, 1994.
40. Standl T., Burmeister M. A., Schroeder F., Currlin E., Schulte am Esch J., Freitag M., Schulte am Esch J., *HES 130/0,4 provides larger and faster increase in tissue oxygen tension compared with prehemodilution values than HES 70/0,5 and HES 200/0,5 in volunteers undergoing acute normovolemic hemodilution*, *ANESTH. ANALG.*, **96** (4), 936-943, 2003.
41. Stockwell M. A., Soni N., Riley B., *Colloid solutions in the critically ill: a randomised comparison of albumin and polygeline. I. Outcome and duration of stay in the intensive care*, *ANAESTHESIA*, **47**, 3-6, 1992.
42. Thompson W. L., Walton R. P., *Circulatory responses to intravenous infusions of hydroxyethyl starch solutions*, *J. PHARMACOL. EXP. THER.*, **115**, 359-64, 1964.
43. Velanovich V., *Crystalloid versus colloid fluid resuscitation: a meta-analysis of mortality*, *SURGERY*, **105** (1), 66-71, 1989 Jan.
44. Vincent J. L., *Fluids for resuscitation; symposium on fluids and electrolytes*, *BJA*, **67** (2), 185, 1991.
45. Vincent J. L., Dubois M. J., Navickis R. J., Wilkes M. W., *Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials*, *ANNALS OF SURGERY*, **237** (3), 319-334, 2003.
46. Vogt N. H., Bothner U., Lerch G., Lindner K. H., Georgieff M., *Large-dose administration 6% hydroxyethyl starch 200/0,5 in total hip arthroplasty: plasma homeostasis, hemostasis and renal function compared to use of 5% human albumin*, *ANESTH. ANALG.*, **83** (2), 262-268, 1996 Aug.
47. Wade C. E., Kramer G. C., Grady J. J., Fabian T. C., Younes R. N., *Efficacy of hypertonic 7,5% saline and 6% dextran-70 in treating trauma: a meta-analysis of controlled clinical studies*, *SURGERY*, **122**, 609-616, 1997.
48. Weeks S., *Reflections on hypotension during Cesarean section under spinal anaesthesia. Do we need to use colloid? Editorial*, *CAN. J. ANESTH.*, **47** (7), 607-610, 2000 Jul.
49. Wilkes M. M., Navickis R. J., *Patient survival after human albumin administration: a meta-analysis of randomised controlled trials*, *ANN. INTERN. MED.*, **135** (3), 149-64, 2001.