Volume Therapy – Colloid Solutions

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Introduction

This review attempts to give an overview of processes influenced by the choice of fluid therapy. Questions like "Can manipulation of fluid resuscitation influence the inflammatory response to injury and organ function" will be addressed. Results of randomised controlled prospective clinical studies suggest that limiting the sodium and chloride input and optimal use of synthetic colloids, which are well retained in the vascular space, can reduce the inflammatory response to injury and improve organ function.[72]

Morbidity and mortality increase as the patient's haemodynamics deteriorate. Hence plasma volume

replacement strategies are frequently used to normalise circulating volume. In addition to crystalloids, synthetic colloidals are widely used to achieve this goal. Crystalloids have a molecular weight under 30 kDa and are used to hydrate the tissues. Colloids have an average molecular weight above 30 kDa and remain predominantly within the intravascular space.

Table 1 provides an overview of crystalloids and colloids used in Europe. Composition, physical and chemical characteristics of these fluids are given in **Table** 2, which demonstrates the enormous diversity of colloids.

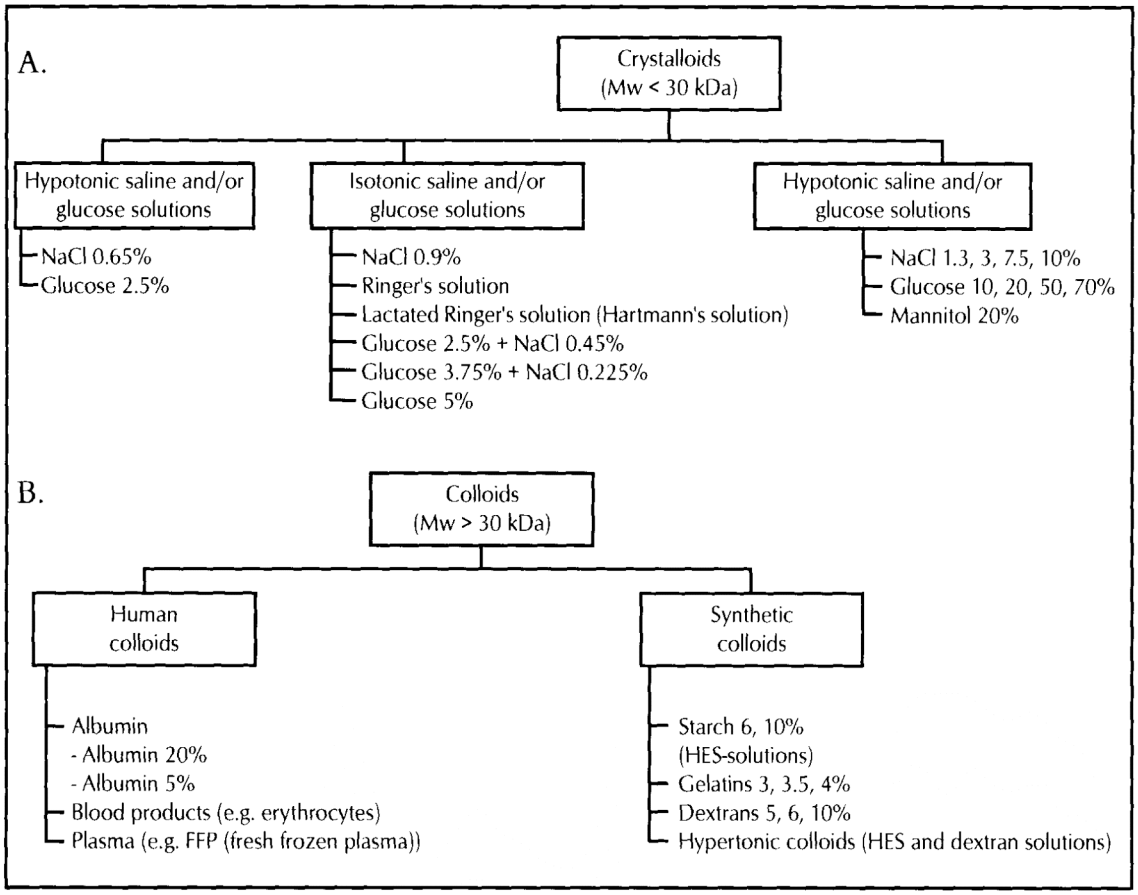

Table 1 A and B. Overview of crystalloids (A) and colloids (B).

	STARCH						GELATIN			DEXTRAN				ALBUMIN
	CORN (MAIZE) STARCH					POTATO STARCH								
Generic name	6% HES 130/0.4	6% HES 200/0.5	10% HES 200/0.62	6% HES 200/0.5	7.2% NaCl with 6% HES 200/0.5	6% HES 130/0.42	Modified gelatin	Modified gelatin	Polygeline	5% Dextran 40	10% Dextran 40	6% Dextran 70	7.5% NaCl with 6% Dextran 70	Albumin
Brand name	Voluven®	HAES-steril® 6% Hemohes® 6%	HAES-steril® 10% Hemohes® 10%	EloHAES®	HyperHAES®	Venofundin	Gelofusine®	Geloplasma®	Haemaccel®	Isodex®	Rheo-macrodex® Gentran® '40'	Macrodex® Gentran® '70'	Rescueflow®	CeAlb®
Supplier Kabi	Fresenius Kabi	Fresenius Kabi B. Braun	Fresenius Kabi B. Braun	Fresenius Kabi	Fresenius Kabi	B. Braun	Braun	Fresenius Kabi	Hoechst Marion Roussel	NPBI	NPBI Baxter	NPBI Baxter	DeVriMed	Sanquin
Active Ingredient	Corn	Corn	Corn	Corn	Corn	Potato	Bovine collagen	Bovine collagen	Bovine collagen	Sugar beet	Sugar beet	Sugar beet	Sugar beet	Human
Colloidal concentration (%)	6	6	10	6	6	6	4	3	3.5	5	10	6	6	20
In vitro mean Mw (kDa)	130	200	200	200	200	130	30	30-65	35	40	40	70	70	69
In vivo mean Mw (kDa) (101,204)	70-80	110-120	110-120	140-150	110-120	Data unknown	-	-	-	-	-	-	-	69
MS*	0.4	0.5	0.5	0.62	0.5	0.42	-	-	-	-	-	-	-	-
C_2/C_n ratio*	9 : 1	5 : 1	5 : 1	9 : 1	5 : 1	6.4 : 1	-	-	-	-	-	-	-	-
Initial volume effect (%)	100	100	145	100 - 110	200 - 400	100	70 - 100	60 - 80	Ca. 70	Ca. 100	200	120	200 - 400	Ca. 300
Volume effect duration (hour)**	3 - 6 (205)	3 - 4	3 (- 4)	8	0.5 - 4	3 - 6	2 - 3	2 - 3	2 - 3	2 - 4	2 - 4	6 - 8	0.5 - 6	2 - 8
Biological $t_{1/2}$	2.8 hours	50 - 70% elimination after 24 hours	50 - 70% elimination after 24 hours	50 - 70% elimination after 24 hours	50 - 70% elimination after 24 hours	12 hours: 50% elimination after 24 hours	A few days	70% elimination after 24 hours	50% elimination after 4 -12 hours	70% elimination after 24 hours	70% elimination after 24 hours	75% eliminaton after 72 hours	75% elimination after 72 hours	17 days***
Polydispersity (kDa) (Mw/Mn)	15 - 380 (2.2)	15 - 750 (2.5)	15 - 750 (2.5)	15 - 550 (3.33)	15 - 750 (2.5)	Data unknown	Virtually mono disperse (1.29)	Somewhat polydisperse (1.55)	Somewhat polydisperse (1.43)	10 - 80 (1.6)	10 - 80 (1.6)	Polydisperse (2.0)	Polydisperse (2.0)	Monodisperse (1.0)
Na^+ (mmol/l)	154	154	154	154	1232	154	154	152	145	154 0	154 0	154 0	1283	154
Cl^- (mmol/l)	154	154	154	154	1232	154	120	100	145	154 0	154 0	154 0	1283	154
K^+ (mmol/l)	0	0	0	0	0	0	0	5	5.1	0 0	0 0	0 0	0	0
Mg^{2+} (mmol/l)	0	0	0	0	0	0	0	1.5	0	0 0	0 0	0 0	0	0
Ca^{2+} (mmol/l)	0	0	0	0	0	0	0	0	6.25	0 0	0 0	0 0	0	0
Lactate (mmol/l)	0	0	0	0	0	0	0	30	0	0 0	0 0	0 0	0	0
Glucose (g/l)	0	0	0	0	0	0	0	0	0	0 50	0 50	0 50	0	0
Osmolality (mOsmol/l)	308	308-310	308-310	308	2464	309	274	295	302	209-330 229-350	323-357 342-378	304-336 324-356	2566	1200
Maximum recommended dose (ml/kg/day)****	50	33	20	20	4	50	None*****	None*****	None*****	26	20	33	4	None

Table 2. Detailed overview of colloidal fluids.

* See Chapter 2A-V.

** Duration of action data is derived from registration documents and based on patient and volunteer data. They should not be compared.

*** For endogenous albumin.

**** Data based on often unpublished and uncontrolled research: not absolute or comparable.

***** Martindale (131) advises a maximum of 29 ml/kg/day.

	500 ml NaCi 0.9% Glucose 2.5% (= glucose-salt	500 ml NaCi 0.45% Glucose 5%	500 ml Ringer's	500 ml Ringer's	500
Na+ (mmoljl)	154	77	0	147.1	130.
Cl- (mmoljl)	154	77	0	155.6	111.7
Glucose (mmoljl)	0	139	280	0	0
Ca^{2}+ (mmoljl)	0	0	0	2.25	1.84
K+ (mmoljl)	0	0	0	4	5.4
M_n2+ (mmoljl)	0	0	0	0	0
Lactate- (mmoljl)	0	0	0	0	28.3

Table 3. Composition of crystalloids commonly used in

Crystalloids

Crystalloids (physiological saline and Ringer's solutions) contribute little to intravascular volume stability. Only 7 to 20%of the administered volume remains within the vascular space after one hour.! Two to six times more volume is necessary, compared to colloids, to achieve the same volume eftect.

Although the volume of crystalloids required to achieve a similar, yet shorter lasting volume effect than that of colloids is many times larger, a study on healthy volunteers required only 1 to 2 times the amount of crystalloids. 155

In general however. a much bigger difference in volume requirement is observed between crystalloids and colloids. This difference is more pronounced in patient populations - compared to volunteers - due to altered haemodynamics, related to increased vascular permeability and anaesthetic techniques.

Colloid osmotic pressure (COP)

The body's fluid is contained in the intracellular. interstitial and intravascular compartments. Intravascular volume can be readily assessed (pulse, blood pressure, wedge pressure. CVP). but interstitial volume can only be poorly measured (skin turgor, and oedema). Intracellular volume cannot be clinically assessed.

Oedema is undesirable as it increases the distance between cells and the capillaries, thus endangering the tissue oxygen supply. Oedema also causes the diameter of capillaries to shrink, thus reducing the supply of oxygen.

Crystalloids migrate to the interstitium rapidly. If glucose 5% is infused, only 7% remains in the intravascular space. When NaCl 0.9% is infused. 20% remains within the circulation. 1 Crystalloids do not contribute to colloid osmotic pressure (COP). but do increase tonicity and osmotic pressure.

Colloids achieve a longer intravascular retention than crystalloids due to their molecular size. Colloids increase COP, depending on the size of the particles (molecular weight), their electrical charge, their molecular shape, their concentration, the level of hyper permeability, their breakdown and their renal excretion.

Colloids

Colloids are defined as substances with a mean molecular weight (Mw) of > 30,000 Dalton. **In** choosing a colloid, potency, side effects and costs are of crucial importance. Synthetic colloidals can be divided into the following three groups: starches, gelatins and dextrans (see **Table** 2).

Depending on the type of colloids, colloids permit decreased blood transfusions, restriction of albumin use, and avoid use of animal substances in medicine (avoid concerns over virus and prion transmission).

Considerable differences of volume effect are seen between crystalloids and colloids and also between colloids themselves. **In Figure 1,** an increase of circulating volume is demonstrated, after an infusion of 500 ml of different solutions in volunteers.

In conclusion, Ringer's lactate and gelatin leave the circulation rapidly, whilst dextran and starch solutions provide considerable volume effect after 2 hours. Hyperoncotic substances attract extra fluid from the interstitial space.

Crystalloid/ colloid controversy *USA vs Europe*

Crystalloid or colloid? This has been a topic of debate for many years. **In** the USA both crystalloids and colloids are used as plasma replacement agents. Currently, only high molecular weight HES solutions (450 kDa or hetastarch) and albumin are available. The FDA didn't approve gelatin derivatives in the USA. Medium molecular weight HES products, as mentioned in **Table 2,** are not commercially available in the USA. This explains the limited use of synthetic colloids in the US. **In** contrast, the human colloid albumin is still administered regularly (although with decreasing frequency). Whilst the USA is commonly regarded as a crystalloid user, colloid - in the form of albumin - is still in common use. **In** the USA there is a need for other synthetic colloids.[183]

In Europe synthetic colloids are the preferred agents to replace plasma,63 but crystalloids remain indispensable for tissue hydration.

Efficacy

Early correction of volume depletion is essential to achieve stable haemodynamics,1 ,20.92, see earlier and to preserve renal function, especially in patients at risk of acute renal failure.[IO] Synthetic colloids are the fluids of choice to correct acute perioperative hypovolaemia,83,123 as considerably more crystalloid would be necessary to achieve the same effect. Colloids reduce the incidence of gut mucosal hypoperfusion compared to crystalloids in cardiac surgery, 141 suggesting a better effect. Also, colloids reduce the risk of gut bacterial translocation and increase blood flow, compared to crystalloids, which stimulates wound healing. 177

Colloid (HES 130) is more effective in terms of haemodynamics and microcirculation compared to crystalloids in models of septic shock.87.124.132 **In** a septic shock model (with concomitant capillary leak) in pigs, fluid resuscitation with HES 130 resulted in maintenance of plasma volume and preserved systemic haemodynamics and oxygenation, compared to lactated Ringer's solution (despite three times more volume being given in the crystalloid group) 132. The use of starch compared to crystalloid furthermore inhibits cytokine production in sepsis by suppressing activation ofNF _B (Nuclear Factor kappa-B) and AP-1 (Activator Protein-1).124

In a near-fatal model ofhaemorrhagic shock in pigs, early colloid infusion resulted in prompt recovery of tissue perfusion compared with crystalloid infusion. This corresponded with increased survival (100% vs 60% respectively).58

In studies with patients undergoing elective abdominal surgery, HES-130 (Voluven®), compared to lactated Ringer's solution, showed better tissue oxygenation and a reduction in inflammatory response (less release of interleukins and adhesion molecules), implying better perfusion and less endothelial damage.[111],112 Similar results were obtained in cardiac surgery, indicating that HES 130/0.4 has a positive effect on inflammation and less fluid is required to maintain haemodynamics.[26] Cardiac function is better preserved by colloid (starch) compared to crystalloids.[6o]

Furthermore the use of colloids (HES 130) does not produce an increase in hyperchloraemic acidosis (base deficit), which was clearly seen after the single use of saline.[26]

Crystalloids can promote a hypercoagulable state with an increased risk of intravascular coagulation.[173]

Type of colloid

It is clear that within the crystalloid/colloid controversy, distinction must be made between the different colloids and crystalloids. Not all colloid data are comparable. **In** Europe the discussion is increasingly focusing on which colloid is preferable (the so-called colloid/colloid debate).27

Costs of therapy

There are many reasons to use crystalloids during surgery, not least the costs.

However, when the overall costs of abdominal surgery using Ringer's lactate, starch or gelatin are compared. they turn out to be similar. and even less costly for colloids.[21J].14R There are significant differences however in administered volumes necessary to maintain filling pressures (11.55 litres for crystalloids. 2.35 litres for starch and 3.35 litres for gelatins). There is also a difference in incidence and severity of hypovolaemia (increase of heart frequency and lower blood pressure).211

As about 4 times more crystalloid is necessary to achieve the same volume effect as new starch solutions.[21J].[149] and because colloids have a positive influence on recovery (see morbidity). colloids have a better cost-benefit profile compared to crystalloids. Cost misapprehension of colloids versus crystalloids is largely based upon the use of albumin. not upon that of synthetic alternatives.

Mortality

In recent years. many meta-analyses have been published. In two of them, colloid-related mortality was compared to crystalloid-related mortality,35,169 and two others compared albumin-related \'lith crystalloid-related mortality.1R5'J. Two of these meta-analyses showed that crystalloids gave the lowest mortality;3R,169 the other two showed no difference in mortality rates . .15.59

The colloid groups of all four meta-analyses comprised albumin only-'R59 or mainly albumin, dextran or blood products.[35].!69 In the latter two, only small trials with more recently introduced

synthetic colloids like gelatins or starch solutions were included. These trials showed a tendency towards improved mortality in the colloid group compared to crystalloids: however. no conclusions should be drawn from these data, due to the small number of patients studied.

In Europe, the use of albumin is decreasing in favour of other synthetic alternatives, for reasons of increased costs. cheaper synthetic alternatives and a possible increased mortality}R.147.190

Whether there is a difference in mortality when treating patients with crystalloids or with colloids remains unknown. For certain goals. categories of patients and research settings, crystalloids seem to be preferable. for other goals colloids are a better option.27·[123]

Morbidity

Research has shown that when fluid strategies are compared, there is a difference in morbidity (such as oedema and pain) to the detriment of crystalloids.[u8],17(,

1. Major electilJe sll1;gery

Gan et al. showed that a group receiving relatively more colloid had improved outcome after major elective surgery.32.65.66.R9 Patients receiving both colloids and crystalloids compared to only crystalloids, had better quality of recovery with lower incidence of postoperative nausea. vomiting, severe pain, and peripheral oedema. us There is evidence that intestinal oedema is associated with impaired gastrointestinal function, impaired tolerance of enteral nutrition, increased likelihood of bacterial translocation. and the development of multiple organ dysfunction syndrome.[7C],·120

2. Caesarean Section

Hypotension IS a frequent problem during administration of local anaesthesitics. and should be avoided as reduced perfusion results in inadequate oxygen supply for mother and child. The use of vasoactive substances should be minimised.

Colloids and crystalloids have been compared during Caesarian section under spinal anaesthesia in several trials. The review article by Morgan[U9] concludes that crystalloids are ineffective in prevention of hypotension.

Colloids lead to significantly less hypotension during Caesarian sections than crystalloids. With colloids the use of vasoactive substances was significantly lower, as was the incidence of postoperative vomiting and nausea. (,j .97.125.174.176.1 *Rl.19.1.1* (JR.!99

With 1 litre HES, hypotension occurred in only 17%, whereas 1.5 litres of Ringer's lactate resulted in hypotension in 75% of patients. 174

3. Paediatrics

A randomised comparison of crystalloids with corn starch derived HES *13010.4* (Voluven®) showed improved quality of postoperative recovery in the colloid group, with a reduced incidence of nausea. vomiting. use of rescue antiemetics, severe pain, periorbital oedema. and double vision. 167

4. Cardiac surgery

When starch was used instead of crystalloid (lactated Ringer's) as the extracorporeal priming solution during open heart surgery, patients showed significantly better results during informative-cognitive testing postoperatively. suggesting that colloid can prevent cerebral dysfunction compared to crystalloid.[9].1

Larger or smaller volumes of fluid

Is it better to give more or to give restricted amounts of fluids? In other words to perform "wet" or "dry" surgery? This discussion resembles the colloid vs crystalloid debate.

The goal of fluid therapy is to maintain tissue perfusion and cellular oxygenation. It is important to avoid underusage of fluid therapy, resulting in hypovolaemia and inadequate tissue perfusion.7[6],77,213 The administration of excess fluid, with its risks of pulmonary and peripheral oedema, should be avoided.7[7]

In a randomised trial performed with 200 ambulatory surgical patients, large (20 ml/kg) and small (2 ml/kg) infusions of isotonic electrolyte solution were compared. The incidence of thirst, drowsiness, and dizziness were significantly lower in the large infusion group at all data points.[213]

Another randomised double blind trial, performed by Holte[88] in 48 patients undergoing laparoscopic cholecystectomy, compared 15 ml/kg with 40 ml/kg lactated Ringer's solution intraoperatively. In this group too, the high volume group showed improved postoperative organ function and recovery, and shortened hospital stay.88 In both trials, the low volume group was undertreated, resulting in hypovolaemia and impaired recovery.88.213

However, as long as patients are not "undertreated", a lower volume can reduce postoperative morbidity.145

The major reason for the observed benefits of restricted fluid therapy may not be solely attributable to crystalloid restriction, but also to the use of colloids instead. With colloids, "dry" surgery can be achieved with maintenance of tissue perfusion (fluid restriction), whilst crystalloid surgery will have to be performed

"wet", resulting in a positive fluid balance post-surgery.99

Most authors recommend a balanced approach to fluid management, with colloids administered to provide haemodynamic stability and maintenance of urine output, and crystalloids administered as maintenance fluids.[99]

In major surgery, patients undergoing colorectal resection were randomised to a restrictive fluid therapy (maintaining pre-operative body weight) or a standard regimen (normally associated with an increase in body weight of 3 to 6 kg). The restrictive group showed a reduction of complications.3[2] The restrictive group received immediately, in case of blood loss, a HES solution, while in the standard group normal saline was infused first. This study merely shows that with optimal use of colloids, the total volume of fluids can be reduced, resulting in a better outcome, and that, in case of blood loss, colloids are the fluids of choice.

Lobo et al[120] did a randomised study in patients undergoing elective colonic surgery comparing restricted « 2 L) or standard (> 3 L) fluid therapy. Restricted fluid therapy was achieved by administration of more colloids. Again the restricted (more colloid based) group performed better. The positive fluid

balance observed after surgery in the standard group resulted in delayed return of gastrointestinal function and prolonged hospital stay.120

2. Colloids

A. Hydroxyethyl starch (HAES or HES)

Hydroxy (A) Ethyl Starch has been manufactured for over 50 years from the amylopectin component of vegetable corn starch. Recently, starch solutions derived from potato starch became available in Europe.

Amylopectin is the osmotically active molecule in a starch solution. It bears a strong resemblance to endogenous glycogen. Thanks to that resemblance, hydroxyethyl starch solutions are well-tolerated and have, compared to other colloids, a low incidence of allergic and anaphylactic reactions.[116] (In part II of this article - which will be published in the next issue of this journal - the side effects of colloids will be further discussed.)

Amylopectin undergoes chemical modification (hydroxyethylation) to make it an effective plasma replacement agent. This chemical modification involves the replacement of the hydrogen (H) atoms by hydroxyethyl groups (CH3CH2OH). Hydroxyethylation increases the volume half-life of the starch, initially only 12 minutes, to several hours.

Hydroxyethyl corn starch solutions are increasingly regarded as prime plasma volume therapy agents[28],m due to the low incidence of side effects combined with good volume effect. Because starches are the colloids of choice in the majority of publications and clinical situations, this article focuses mainly on these colloids replacement agents.

Variation in the chemical structures of starch molecules allows solutions to be formulated that can be geared to specific clinical needs. Starches can be categorised based on their *conantration (I), molecule size (II), polydispersity (III), molar substitution (IV) and substitution pattern (C2/C6 ratio) (V).* These characteristics are of importance to determine the volume effect and the duration of the intravasal stay, as well as the rheological characteristics and side effects of the different HES-products. These chemical HES-characteristics will be elucidated below.

I. Concentration (6 or 10%) *Oncotic effect*

The concentration (meaning the quantity of active substance per unit volume) mainly determines the *initial* volume effect. HES with a concentration of 6% contains 60 grams of starch per litre. Therefore, 500 ml HES 6% contains 30 grams of active substance, whereas 500 ml HES 10% contains 50 grams of starch.

HES 6% solutions are iso-oncotic (one litre replaces one litre of blood loss); HES 10% solutions are hyperoncotic (replacement as above plus additional fluid drawn in from the interstitial space). Hence 10% HES 200/0.5 has a volume effect of 145%. Tlus hyperoncotic effect might be advantageous in situations where interstitial fluid restriction is desired (194). (In some European countries other HES concentrations are available).

Tonicity

0.9% NaCl is the carrier solution for all starch products except HyperHAES, meaning they are isotonic (independent of their oncotic effect).

HyperHAES is an iso-oncotic, hypertonic (7.2% NaCl) solution. 10% HES 200/0.5 is an isotonic, hyperoncotic solution.

II. Mean molecular weight (Mw) (130.000 or 200.000 Dalton)

The starch solutions available in Europe are of medium average molecular weight (MMw) (130,000 and 200,000 Da). In other countries. other starch solutions with a molecular weight varying trom 40.000 Da (LMw - low molecular weight) up to 480.000 Da (HMw - high molecular weight) are available.

Molecular weight influences a solution's pharmacokinetic profile. Larger starch molecules circulate longer than smaller starch molecules, as it takes longer for them to be broken down into molecules that are small enough to pass the renal membrane.

Compared to low (about 70,000 Da) and medium (130,000-20,000 Da) molecular weight starch solutions. high (circa 450.000 Da) molecular weight starch solutions can considerably lengthen bleeding time (7,192). Large. breakdown-resistant starch molecules also influence plasma viscosity and deternune the level of tissue storage. As a result of these properties, high molecular weight solutions (450,000 Da) do not improve rheology. They are no longer used regularly in Europe. A recent publication of Neff et al[143] has shown that a lower molecular weight starch (130 kDa) has an important positive influence on rheology (blood viscosity and erythrocyte a&!1;regation) compared to higher molecular weight starches (200 kDa).

Besides the mean Mw. also the distribution of molecular weights (see 2A-III) within HES solutions influences the effect on coagulation and the level of tissue storage.

In vitro and in vivo molecular weight

A disctinction between the in *vitro* and the in *vivo* molecular weights of starches should be made.

The in *vitro* molecular weight is the average molecular weight within the solution prior to

infusion. The in *vivo* molecular weight is the mean molecular weight after infusion - infused starch molecules are enzymatically degraded whilst renal clearance of small molecules is underway. Starch molecules are broken down in the circulation by amylase until they can pass the kidney filter and leave the body in the urine. A starch product with relatively large, hard-to-degrade molecules, will have a high in vivo molecular weight whereas a starch product with relatively more smaller, easy-to-degrade molecules, has a low in vivo molecular weight. In addition to the initial molecular weight (in vitro molecular weight), both molar substitution (2A-IV) and the C2/C6ratio (2A-V) will influence the in vivo molecular weight.

Lower in vivo molecular weights are associated with less accumulation in plasma and less influence on coagulation.[111]1. (see below)

The in vivo molecular weight of HES 200/0.62 is 140-150 kDa, that ofHES 200/0.5 is 110-120 kDa and that ofHES 130/0.4 is 70-80 kDa (101,204). The in vivo molecular weight needs to be above the kidney threshold to provide volume efficacy. In vivo molecular weight deternunations may provide slightly different values mainly due to variation in technique.1'J2 (Table 2)

III. Polydispersity (distribution of molecular weights: 15.000-380.000, 15.000-550.000 or 15.000-750.000 Dalton)

HES solutions do not only consist of molecules of one single size. The molecular weights listed in Table 2 and 2A-II refer to the *average* molecular weight. In a solution of for example 200.000 Da. both smaller and larger molecules occur. Every HES solution has a certain degree of polydispersity. or range of molecular weights.

Although larger starch molecules provide a longer duration of action, they are also responsible for side effects such as the influence on coagulation. An optimal balance needs to be achieved.

After HES 200/0.5 another short acting starch became available - HES 130/0.4. Research projects have established that the combination of chemical characteristics in corn HES 130/0.4 generates the same volume effect as corn HES 200/0.5. Both corn solutions provide a volume effect of 100% for a couple of hours. The initial volume effect is however somewhat greater and more rapidly achieved with HES 130 than HES 200.[1811] Conversely. the influence on coagulation parameters and coagulation time is less when using HES 130/0.4; this contributes to reduced blood loss and decreased transfusion requirements compared to HES 200/0.5. Where a medium-long acting standard plasma replacement agent is needed, HES *130/0.4* is preferred.

Some HES products have a higher polydispersity than others. The molecular distributions of starch solutions available in Europe are represented in **Figure** 2.

The peak of the curve indicates the *weighted* average of all molecular weights in the solution (130 or 200 kDa). This is called the mean molecular weight of the solution in question. Heavier starch molecules contribute relatively more to the mean Mw than lighter starch molecules. Differences in the curve heights of starch products are seen because one solution has a wider range of molecular weight (is more disperse) than

another. Moreover. HES *130/0.4* contains more molecules per volume unit than HES *200/0.5* and HES *200/0.62* - i.e. a 130.000 dalton 6% solution (60 grams per litre) contains more molecules than a 200,000 Dalton 6% solution.

Because HES solutions are polydisperse, a stable volume effect is generated. This so-called plateau effect is shown by plasma volume measurements. The mechanism thereofis explained in **Figure** 3. Thanks to the plateau in the volume effect, a rapid and long lasting reponse is achieved (depending on the HES product used, this may vary from about 3 up to 36 hours.

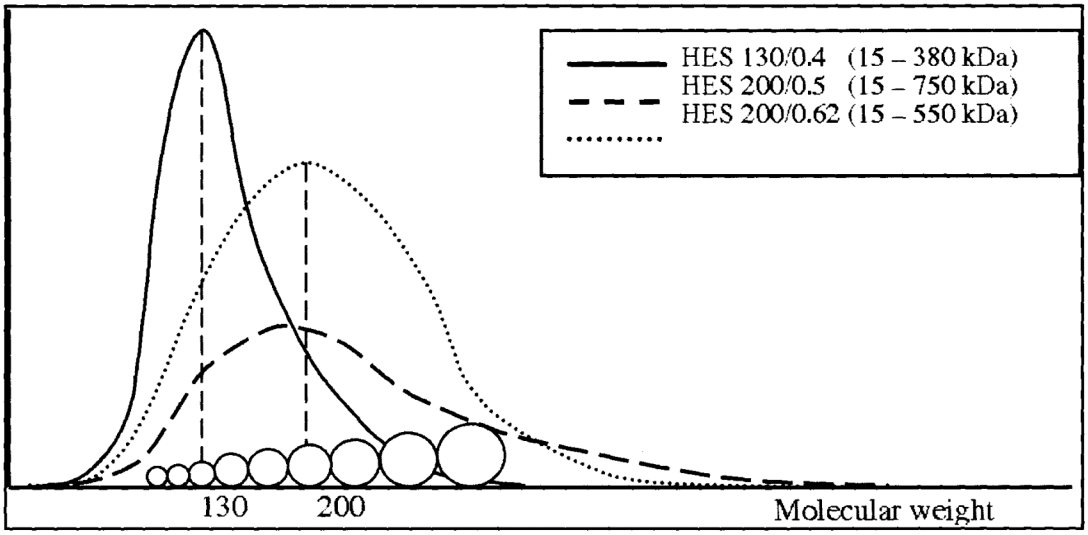

Figure 2. Schematic representation of polydispersity (Mw in kDa) of HES products available in Europe.

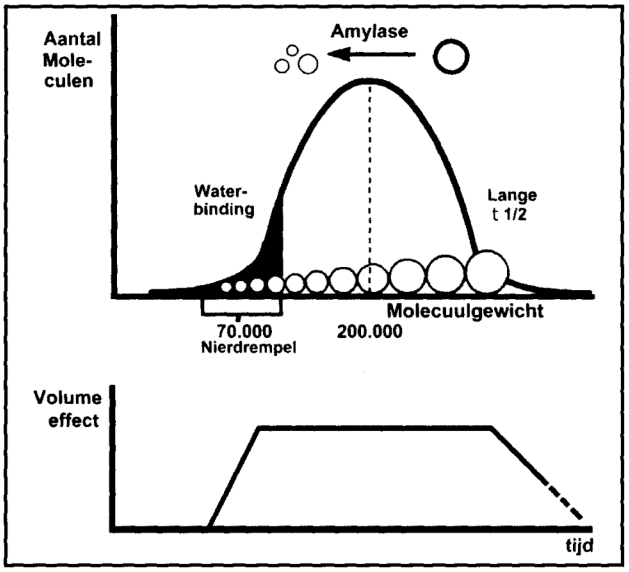

Figure 3. Mechanism of action of HES.

1. The volume effect of HES is caused primarily by water binding to small starch molecules.
2. Small molecules are excreted; larger circulating molecules are 'cut' by the enzyme a-amylase.
3. Renal excretion of molecules keeps pace with the generation of new smaller molecules by amylase activity. These again bind water, maintaining the volume effect.
4. This plateau volume effect, which is only seen with starches, provides haemodynamic stability.

IV. Molar substitution (MS) and degree of substitution (DS)
(MS from 0.4 to 0.62 - 40 to 62% / DS from 0.4 to 0.5 - 40 to 50%)

HES is a polysaccharide comprising glucose molecules, and is hydrolysed in the circulation by a-amylase. This process is represented in Figure 3. The previously described hydrox)'ethylation of glucose molecules inhibits enzymatic breakdown by amylase, prolonging the intravascular effect. Different HES products have different levels of hydroxy ethyl at ion.

As a reaction to HES administration, the amylase level is temporarily increased.(,J

Molar substitution (MS) means the percentage of hydroxyethyl groups per starch molecule. (Example: MS of 0.4 means that 40%) of all glucose molecules carry a hydroxyethyl group).

Molar substitution influences the HES elimination characteristics. More highly substituted starches are broken down more slowly by amylase. This prolongs intravascular retention of hydroxyethyl starch. A highly substituted HES solution remains within the circulation for a longer period of time due to the slower breakdown compared to a lower substituted solution. An example thereof is HES 200/0.62, which is longer acting than HES 200/0.5 because of its higher MS (192). HES 450/0.7 has an even longer volume effect.[911]

Starches with a higher MS produce a slower volume response. A trial has been performed comparing 6lJ'6 HES 650/0.7 with 6% HES 130/0.4. The lower substituted starch was shown to have superior volume effects as HES 130/0.4 is rapidly cleaved by amylase to a size that is osmotically active. but still higher than the renal threshhold. HES 130 thus generates more particles more quickly which results in a higher initial volume effect. Slower breakdown of the high Mw-molecules with high MS in the HES 650 group results in a delayed

volume effect. This results in a significantly superior volume effect and systemic blood pressure response in the HES 130/0.4 group.95

The degree of substitution (DS -Degree of Substitution) is a term related to MS, but less often used. It indicates the percentage of starch molecules carrying one or more hydroxyethyl groups. For illustration purposes, Figure 4 shows an example of the MS and the DS.

Where a longer acting starch is needed (lengthy surgical procedures or in postoperative patients), administration of HES 200/0.62 is preferred to the shorter acting HES 200/0.5 or HES 130/0.4.

V. Substitution ratio (C_2/C_6 ratio)

Duration of action is determined not only by the number of substitutions, but also by the site of substitution, i.e. carbon atom within the glucose sub-unit to which the hydroxyethyl group is attached. Hydroxyethylation can take place on C_2 or C, (see Figure 5).

The ratio between both possible substitution locations is represented by the substitution ratio (C)C" ratio).

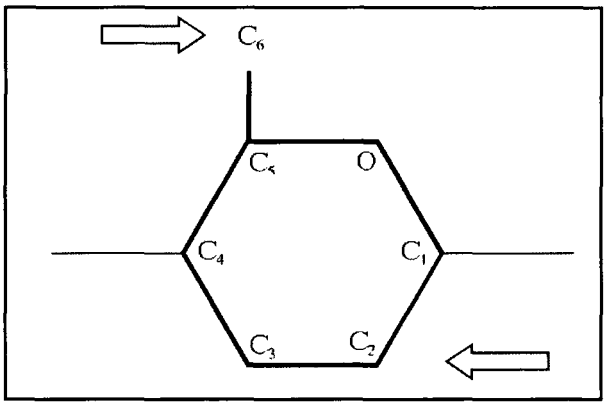

Figure 5. Hydroxyethyl substitution sites on the glucose sub-units of the starch molecule: C_2 and C_6 (indicated by arrows).

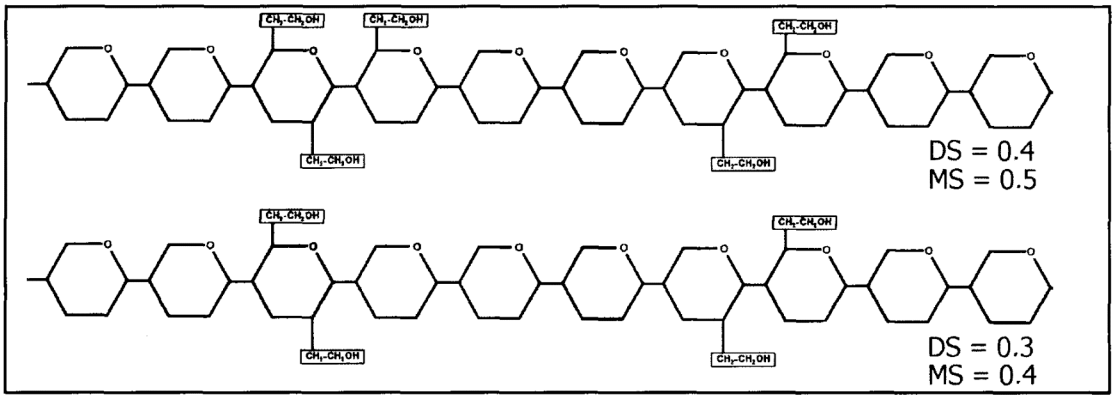

Figure 4. Schematic representation of the MS and the DS of two HES products (A. HES 200/0.5 B. HES 130/0.4).

Hydroxyethylation (substitution of an H atom by a hydroxyethyl group) at the C2, position will, due to greater protection from amylase attack, result in a longer duration of action than a substitution at C6′ This is due to the stereochemistry of the starch molecule hindering amylase attack at this site.

Hydroxyethylation at the C2, position provides strong protection against degradation by amylase by means of a strong steric inhibition of the enzyme. Hydroxyethylation at Co on the other hand,

produces less protection from amylase.

Starches with a higher *C2/C6* ratio, achieve a longer lasting effect even when the molecular substitution (MS) and molecular weight (Mw) are lower. As an example, HES 130/0.4, notwithstanding a lower Mw and lower MS, has the same duration of action as HES 200/0.5 thanks to its higher C)C" ratio. This higher C)C, produces a more efficaciou.s starch, so that even with lower Mw and MS the desired duration of volume effect is achieved.

VI. Origin: corn (maize) or potato.

Hydroxyethyl starch solutions have been manufactured from the amylopectin part of vegetable corn starch for over 50 years. Recently, a starch solution derived from potato starch became available in Europe, resulting in confusion amongst users and pharmacists. The generic names are similar - 6%, HES 130(0.4 (Voluven®, corn) or *6'Y"* HES 130(0.42 (Venofundin®, potato), suggesting that both products have the same ingredients and characteristics. Also the registration document doesn't mention the origin of the solution. However. there are differences, also at molecular level. between both products. summarised in Table 4.

Both the MS (0.4 vs 0.42) and the C,(C" ratio (9:1 vs 6.4:1 respectively) are different.

Amylopectin is the osmotically active molecule in a starch solution. The potato-derived HES 130 solution contains less amylopectin than a HES 130 starch solution (about 80/)1, and 99% respectively), and this may alter the volume effect achieved. Starch solutions also contain some amylase (about 20% and 1 % respectively), which is unbranched and has a lower water binding capacity than amylopectin.

The SPCs (Summary of Product Characteristics) of both products contain major differences which should be taken into account. and are important for practical and legal aspects. In contrast to potato HES 130(0.42, corn HES 130(0.4 is registered for usage in children. has no limitation of infusion rate and can be administered at high pressure (important aspects in emergency settings and operating theatres). does not require blood sampling to ensure correct blood typing before administration (important in emergency departments). and is not contra indicated in patients with impaired liver function (important in ICU setting).

Physicians should be aware of the official SPC indications and contra indications for drugs and realise that they can be criticized for using them in off-label applications if problems arise .178

There are over 70 clinical publications with the corn product, but only 2 with the potato product. HES 130(0.4 from corn has been shown to be safe in numerous situations, including paediatrics, impaired kidney function and high dosage. Stability data are available for storing corn starch at both low and elevated temperatures.

There are few studies ''lith potato derived starches (HES 130/0.42). There are. in contrast to HES 130 derived from corn, no publications on allergic reactions. embryotoxicity, pregnancy, accumulation, toxicology, impaired kidney function, high dosage, repeated infusion over several days, cardiac surgery. orthopaedic surgery. acute normovolemic haemodilution, patients with head injury. paediatrics. stroke. and usage in elderly patients. Venofundin® was withdrawn from registration in Spain and France.

Evidence exists that potato starches impair coagulation more than corn starches.[96] To date only one clinical study has been published on potato HES 130. showing no advantages compared to HES 200/0.5.[165] In contrast. corn HES 130 has proven superiority over HES 200(0.5 in several clinical trials62.63.1 01.1 112.1 U and in in vitro studies.

VII. Summary

The clinical effect of a starch solution derives from a balance of all the characteristics mentioned above (concentration, Mw, polydispersity. MS, OS and C,(C,' ratio). Table 5 describes how these characteristics determine the volume effect.

Concentration determines the volume effect. The Mw, the MS, the OS and the C,(C" ratio determine the *duration* of the volume effect. A product with a high concentration. but with a low molecular weight, a low molar substitution. a low degree of substitution and a low C,/C" ratio will have a potent, yet short-acting effect.

The characteristics of a starch solution can determine the strength and speed of the initial volume effect. A 691J 130.000 Da starch contains more particles than a 691) 200.000 Da starch. Thus the initial volume effect of the lower Mw solution is greater. 1811 A 6% HES 70/0.5 solution contains even more particles than 6% HES 130(0.4. but has a lower initial volume effect, because a large proportion of smaller starch molecules will be rapidly eliminated by the kidneys, reducing efficacy and preserving oxygen supply less well compared to HES 130. ISO

Over time. the search for the ideal starch solution has lead to the development of different HES products. all with their own unique profile.

Different starches are best suited to different indications: see Table 6.

The different starches also have different licensed dose maxima. Long-acting starch (HES 200/0.62) has a maximum dose of 20 ml(kg(day (about 1500 ml for a patient of70 kilos).

HES 130/0.4 has a maximum dose of 50 ml/kg/day (about 3500 ml for a patient of 70 kilos). Practically, short-acting corn starch products (like HES 130/0.4) can be used (almost) whenever needed (SPC HES 130/0.4 (Voluven®).

	High	Low
Concentration	Potent volume effect	Low volume effect
Molecular Weight	Long-acting Slower onset	Short-acting Quick onset
Molar substitution (MS) and degre of substitution	Long-acting	Short-acting
C2/C6 ratio	Long-acting	Short-acting

Table 5. Intluence of HES characteristics on the volume effect.

Gelatin

Gelatins are synthesised from hydrolised bovine collagen. Gelatins are protein chains comprising mostly glycine. proline and hydroxyproline. Gelatins are relatively rapidly excreted by the kidneys after infusion.

Gelatins are the oldest plasma replacement agents.

They were first used to treat shock in 1915, and during the First World War they were used widely. Although gelatins are in common use in some European countries,

they were banned by the FDA in the USA in 1978, because of the high incidence of allergic reactions.[17],55 The quality of gelatin products has improved thanks to a change in the production process, but they have not been reassessed by the FDA.
Allergic reactions to gelatins are due to the release of histamines. When patients are pre-treated with histamine blockers, the release of histamine may be inhibited.

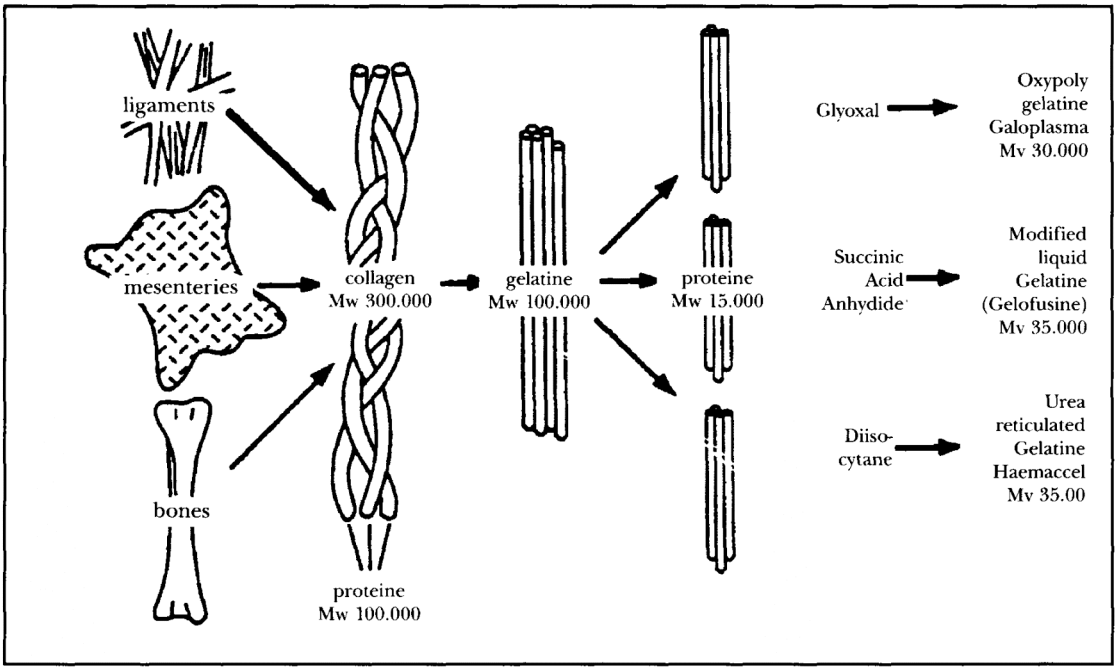

Figure 6. Schematic representation of the production of gelatin-based plasma replacement agents.

SHORT-ACTING HES		LONG-ACTING HES	HES WITH POTENT VOLUME EFFECT	
6% HES 130/0.4	6% HES 200/0.5	6% HES 200/0.62	10% HES 200/0.5	6% HES 200/0.5 in 7.2% NaCl
• Before and during short operations • During long-lasting surgical operations with blood loss		• Prior to longer operations • During longer surgical procedures without blood loss		• 'Small Volume Resuscitation' • For acute hypovolaemia
Recovery: • Rapid postoperative stabilisation		**Recovery:** • Prolonged postoperative stabilisation • For hyperpermeability		
ICU/Nursing ward: • For blood loss • Large volume requirements • Prolonged use (> 1 week)		**ICU/Nursing ward:** • Prolonged haemodynamic stabilisation (without blood loss) • For hyperpermeability		**ICU:** • Raised intracranial pressure • Acute hypovolaemia • Oedema
Emergency: • For hypovolaemia				• 'Small Volume Resuscitation' • Acute hypovolaemia • Head injury
Cardiac surgery • Priming of extracorporeal circuit*			**Cardiac surgery:** Priming of extracorporeal circuit*	
Dialysis: • Prevention and treatment of hypotension				

Table 6. Indications for the different HES products available in Europe.

* To prime the extracorporeal circuit during cardiac surgery, it is advised to use a fluid of 3 or 3.75% short-acting HES. Example of a 3% priming fluid: 1 litre of 6% HES 130/0.4 plus 1 litre of crystalloid.[63] Example of a 3.75% priming fluid: 750 ml of 10% HES 200/0.5 plus 1250 ml of crystalloid.[188]

Gelatins have a relatively low molecular weight (30-35 kDa) and thus a relatively short duration of action. In most studies the volume effect is maximal 70 to 80')1) of the infused volume and lasts for up to 2 hours. Because of the relatively short effective period (due to rapid glomerular filtration) gelatins are generally not seen as the ideal solution to replace blood loss during an operation. 17

Gelatins can influence the level of plasma fi bronectin)4.197

Gelatins can be infused almost without dose limitation, but too much haemodilution must be prevented. Haemaccel® however, does have a dose limitation because of its high level of calcium. The maximum is one and a halflitres per 24 hours.

Research shows that gelatin derivatives, as well as other synthetic colloids, can exert a negative influence on coagulation (part II. 2-II) and possibly wound healing. 53.1 H5

Allergic reactions are observed more frequently after infusions with gelatins than infusions with other synthetic colloids (Figure 8).

Interaction with proteinuria definitions

Gelatins may give rise to incorrect results from urine analysis. Gelatins are small proteins and can cause a false positive proteinuria result. Cases have been reported in which a functioning kidney was refused for transplantation, because the potential kidney donor underwent volume resuscitation with gelatins. This is not seen when starch or dextrans are used.[42]

Gelatins and vegetarians, Hindus, and Muslims

Religious as well as personal considerations can be of importance when choosing a colloid: Hindus do not allow bovine derived products, while Muslims avoid porcine derived products.[511] Most vegetarians avoid intake of all animal derived products.

A gelatin solution can be either of bovine or porcine onglll.

With alternative colloid preparations readily available. it is not difficult to be sensitive without violating the patients' beliefs or principles.[511].[1]('('.1[H]4

Prion diseases, BSE, vel and gelatin

Prion diseases are disorders of human and animal nervous systems, marked by degenerative changes in the brain with a fatal outcome. The current hypothesis is that they arise from the conversion of the normal cellular protein (PrPC), expressing itself in a number of cell types,

into an abnormal protein (PrPSc or PrPRes*). This is an irreversible conversion in the structure of the Prpc, a socalled 'winding error'. The exact function of the protein is unknown, but it probably plays a role in copper metabolism. In the eighties, the United Kingdom identified prion disease in almost 200,000 cattle (so called bovine spongiform encephalopathy - BSE or 'mad cow disease'. Since then, BSE has been detected in most European countries, but in smaller numbers than in the United Kingdom. BSE has also been diagnosed in cattle in Canada, the USA and japan. In addition to BSE in cows and scrapie in sheep (both prion diseases), TSE (Transmissable Spongiform Encephalopathy) has recently been diagnosed, outside the laboratory setting, in goats. In February 2005 the European Committee for animal health decided that goats will also have to be tested routinely for the presence ofTSE.

Creutzfeldt jakobs disease (CJ) is a similar disease occurring in man. Cj had a stable incidence of one per one million person years. In 1996 hmvever. a new form of Creutzfeldt jacobs disease was found: the variant Creutzfeldtjakob (vCJ), a disease in young people, with a far poorer prognosis and a much more aggressive course. After the initial symptoms, the average life expectancy is only one year. The incidence of vCj appears to be on the increase. Up to june 2005, a total number of 170 cases of vCj have been diagnosed, of which 155 were in the United Kingdom. The other patients were from japan, the United States, Canada, Ireland, France and the Netherlands**. Estimates of the total number of vCj patients to be infected range from a few dozen to many thousands. Evidence exists that the BSE-prion is responsible for generating both BSE and vCJ.2111

In addition to the nervous system, organs such as the spleen, the entire gut, lymph nodes, appendix and tonsils can harbour prions.[2].[85] Transmission of vCj is not only possible from eating infectious material, but iatrogenic vCj transmission through endoscopic procedures. surgical procedures and blood and tissue donations have been recorded and thus need the same precautionary measures and attract the same public health concerns. The incubation period after intravenous transmission of TSE seems to be much shorter than after oral infection. H5

Some years ago the possibility of BSE transmission (Bovine Spongiform Encephalopathy) through gelatin administration (both orally and parenterally) was raised. BSE and vCj are both prion diseases. Human infection with BSE might lead to the development of the human form ofBSE, the so-called vCJ or the Creutzfeldtjakob

variant. However, the risk is a theoretical one, which to this day has not been identified clinically. **In** a publication by Laubenthal t!4 the risk of transmission of the bovine spongifonn encephalopathy by gelatins is assessed at less than 1: 1,000,000. 'The Gelatin Manufacturers of Europe' (GME) states that in the present process of gelatin production, no BSE pathogens are detectable even if infected raw material is used.[6s]

However. the European COImnittee advises that the use of animal products in medicine should be avoided where alternatives are available. **In** this respect, one should be aware of the origin of gelatin solutions.[77]

Recently it has been proven that prion diseases can be translnitted by blood transfusions. This already was shown in a laboratory setting. but Llewelyn et al.[119] published a case of vCl in a blood-transfusion-donor who had deceased after the blood-transfusion-recipient had deceased of vCl two years previously. **In** several countries this lead to a refusal of blood-donors who had previously received a blood-transfusion. Also several countries are banning donors from regions with a high prevalence of BSE. These measurements reduced the blood-donor-population conciderably, which made the availability of blood even more scarce.

Because of the risk of transmission of prion diseases by blood-transfusions, over the last years many countries have implemented leucodepletion of blood units. Nobody knows whether leucodepletion is sufficient, or even necessary, for protecting transfusion recipients from vCl prions. Leucoreduction is efficacious in reducing white-cell-associated transmission of spongiform encephalopathies, but fails to eliminate it,74

However, all these measures made blood-transfusions even more expensive (and possibly more safe).

In addition, some infectivity of TSE's is assumed to be plasma associated.[74] The policy of leucoreduction aimed at reducing TSE infectivity may require reevaluation.

C. Dextran

Dextrans are made from sugar beet; sugar molecules are polymerised by bacteria activity, producing a polydisperse mixture of glucose polymers. Dextrans have molecular weights ofl, 40 and 70 kDa. Dextran 40 in 5% solution is iso-oncotic. A 10% dextran solution has hyperoncotic characteristics and is a plasma expander (volume effect over 100%). *m1)* Dextran 70 is iso-oncotic. Dextran 70 has larger molecules than dextran 40, and hence remains in the circulation for a longer period of time.

Dextrans may interfere with blood group assessment (part **II.** 2-IV). Dextrans can also influence biochemical tests, such as plasma glucose and protein levels.[207]

Dextrans are still used in Scandinavian countries.

Outside Scandinavia, dextrans are now rarely used in Europe. Within Scandinavia the use of dextran preparations is decreasing rapidly. Dextrans are no longer the dominant colloids in Sweden; a majority of hospitals have switched to starch preparations. so

However, some dextran use persists, mainly in vascular or plastic surgery. because of the alleged positive influence on rheology. However, research has revealed that dextrans have a negative influence on rheological factors such as viscosity and deformability of erythrocytes.[u6]

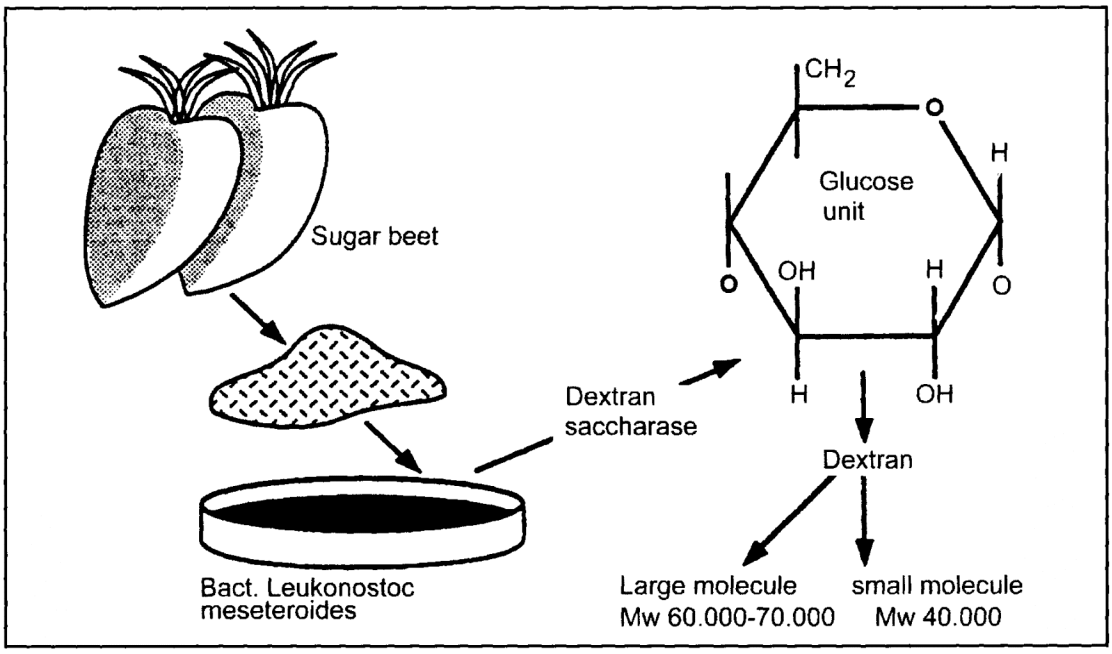

Figure 7. Schematic representation of the production of dextran-based plasma replacement agents.

In fact there is no longer any indication for administering dextrans. Better alternatives, like starch products, are available, and they do not have the disadvantages of dextrans such as allergic reactions and coagulation complications (part II).

D. Albumin

Albumin is a human colloid, available as iso-oncotic (5[illegible]) and hyperoncotic (20(J1»)) solutions. The molecular weight of albumin is 69.000 Dalton.

Albumin was the colloid of choice for many years. but today this is certainly no longer the case in Europe. In many countries. it is generally accepted that there is now no place for albumin in surgical and ICU patients.·[1]1.44.1911 Cost is a major reason - albumin is expensive. Outcome benefits have not been shown in hypovolaemic or in hypoalbuminaemic states.[16.19] . .1R.711 In contrast. in conditions

with increased vascular permeability. leakage of albumin into the interstitial space can aggravate oedema formationJII.1Il6

AnalbIlminaemia is a hereditary condition in which albumin cannot be produced. People with analbuminaemia have no or very few pathophysiological symptoms. The condition is often silent.[129]

Even in patients with a very low albumin level «5g/l). albumin administration does not show improvement when compared with synthetic colloids. Although albumin has a transport function for several drugs and endogenous substances such as bilirubin and free fatty acids, a low albumin level does not appear to have a negative eftext.

In Europe. albumin has been mostly replaced by synthetic colloids - mainly starches and gelatin derivatives. Synthetic alternatives are at least as effective as albumin. when administered in ICU and in the operation theatre (including priming of the extracorporeal circuit).IHH

A meta-analysis published m 1998 showed that albumin may also have a negative effect on surviva],JR Possible causes for tllis have been debated at length, perhaps increased oedema due to capillary leak leads to poorer pulmonary function, a more serious inflammatory reaction and decreased gas exchange.[lOll] This metaanalysis led to the initiation and publication of a large multicentre trial[o9] comparing the safety of albumin and normal saline. In this trial. albumin had no impact on survival, nor did crystalloids. In the trauma subgroup crystalloids seemed to have a somewhat better outcome, in the sepsis/ICU subgroup albumin seemed to have some advantages. However. the SAFE study did not give us reason to start using albumin again or to increase its use.

The availability of synthetic colloidal alternatives also argues against the continued use of albumin. Synthetic colloids are more cost-effective and are often safer and more effective than albunlin. **It** should be remembered that these advantages were demonstrated before the mortality discussion began.

There are now only a few residual indications for albumin: treatment of patients with burns, in neonatology and in plasmapheresis procedures.

Although research has been conducted with synthetic alternatives in most of these areas. albumin often remains preferable due to the larger level of experience with it. It is expected that the use of albunlin will further decrease as more data on synthetic colloids become available in these indications.

3. Hypertonic colloids

Hypertonic fluids tor "Small Volume Resuscitation" (SVR) need to be reviewed separately.

Hypertonic fluids are attracting considerable attention in research and during scientific meetings.

These solutions have been researched for over 20 years. In spite of promising results, there is lack of clarity regarding the optimal policy in case of trauma: quantity of fluids to administer. time of fluid administration (early or late) and aiming for a higher (100 mmHg) or lower (70 mmHg) systolic blood pressure. 1111

Indications for these fluids are restricted to specific situations. The use of hypertonic colloids seems justified in cases of neurotrauma with hypovolaemic/haemorrhagic shock. Hypertonic colloids are the only fluids able to correct hypovolaemia whilst decreasing intracranial pressure.

SVR is performed with hypertonic iso-oncotic solutions, i.e. a small volume (250 ml) of concentrated NaCl (7.2 to 7.5%) plus colloid *(GlY0).195*

Rapid infusion of 250 ml of such a solution results in a volume effect up to 400% (about 1000 ml) and can replace 2 litres of blood loss. 1411 In addition to the infused volume of 250 ml, extra fluid is pulled from the interstitium thanks to the high concentration of NaCl. If the patient is poorly hydrated, the volume effect will be less than 400%.

A hypertonic solution without colloid will produce a rapid increase in volume as well, but when a colloid is added to the hypertonic solution. the effect will last considerably longer. Dextrans and hydroxyethyl starches derived from corn are the colloids used to achieve this.[m]

Compared to hypertonic saline solutions, hypertonic colloids have an additional effect on inflammatory reactions,146 resulting in improved vascular condition. Claimed additional effects of the colloid are:

- Increased capillary vascularisation
- Decreased reperfusion damage (less endothelial
  oedema and vascular permeability) - Decreased leucocyte adhesion
- Decreased bacterial translocation

Safety of hypertonic colloids

In a publication from Austria, the safety of hypertonic starch solutions was assessed. From 1991 to 2000, a total of 56,000 units have been administered to 18,500 to 37,000 patients (1.5 to 3 units per patient). The incidence of allergic reactions appeared to be only 0.00012[C]}fl. The conclusion is that hypertonic starch solutions can be used safely in day to day practice.134.170

The colloid component (HES 200/0.5) was shown not to reach the cerebrospinal fluid in patients with disturbed blood-brain barrier function after subarachnoid haemorrhage or head trauma.[4R]

Svensen[1R2] concluded that. from the vast amount of work on hypertonic solutions, they seem to be very safe. In 35 clinical trials, more than 1400 patients have received hypertonic solutions without any complications.[182] *Indications for hypertonic colloids*

A. Trauma patients
B. Cardiac and aortic surgery
C. Increased intracranial pressure (ICP)

D. **In** *trauma patients:*

E. Trauma patients suffering from haemorrhagic shock: resuscitation with a hypertonic solution resulted in quicker haemodynamic improvement137.153 and a decrease in mortality compared to standard treatment: a meta-analysis. analysing 8 preclinical studies companng hypertonic solutions to standard treatment revealed that hypertonic colloids significantly decrease mortality. This is also the case in the subgroup of patients with penetrating trauma.[202] Clinical results suggest that hypertonic solutions may be of value in acute hypovolaemia, provided they are given before standard fluid resuscitation,72.134.152

II. Trauma patients suffering from severe head injury seem to benefit most from hypertonic solutions in the pre-hospital setting.[182] When hypertonic starch is administered after head injury in rats the intracranial pressure immediately decreased compared to normal saline. Significant improvement of perfusion and markedly reduced structural damage was seen after small volume resuscitation with a hypertonic starch. 186

Recently, guidelines have been published in the Netherlands on the indications for hypertonic colloids in traumatology. 54 These guidelines, which are summarised in Table 7, are based upon European practice - in contrast to the ATLS®*, which is based upon American practice. The situation in Europe differs to the US situation with respect to:

1) available colloids;
2) time to get to a hospital;
3) type of injury (penetrating or not);
4) level of education of ambulance personel.

B. For cardiac and aortic surgery:

Supervised peri operative administration of a hypertonic solution improves cardiac performance and decreases the need for additional volume replacement and possibly decreases blood loss. Postoperatively, treated patients show a better (which means less positive) fluid balance.[13],37.153

C. In increased intracranial pressure (ICP):

Hypertonic colloids can effectively decrease ICP, even in therapy-resistent patients who do not react to mannitol. No rebound effect is observed, contrary to treatment with mannitol.[9].[82] This may be explained because the colloids in the hypertonic solution can bind fluid drawn from the interstitial space. The large colloid molecules remain within the vascular space for a longer period of time, whilst the very small (crystalloid) mannitol molecules can pass into the interstitial space or be excreted by the kidneys. Bentsen infused a hypertonic starch at a dose of 2 ml/kg to critically ill patients suffering from increased intracranial pressure due to subarachnoid haemorrhage. He concluded that this therapy is safe and effective, leading to predictable and clinically significant beneficial effects on rcp and cerebral perfusion pressure. The effect was still present 3 hours after end of infusion. [9] In another clinical trial, 6%) HES 200/0.5 in 7.2% NaCl HyperHaes proved to be more effective than mannitol in 15% in neurosurgery patients with an increased ICP.

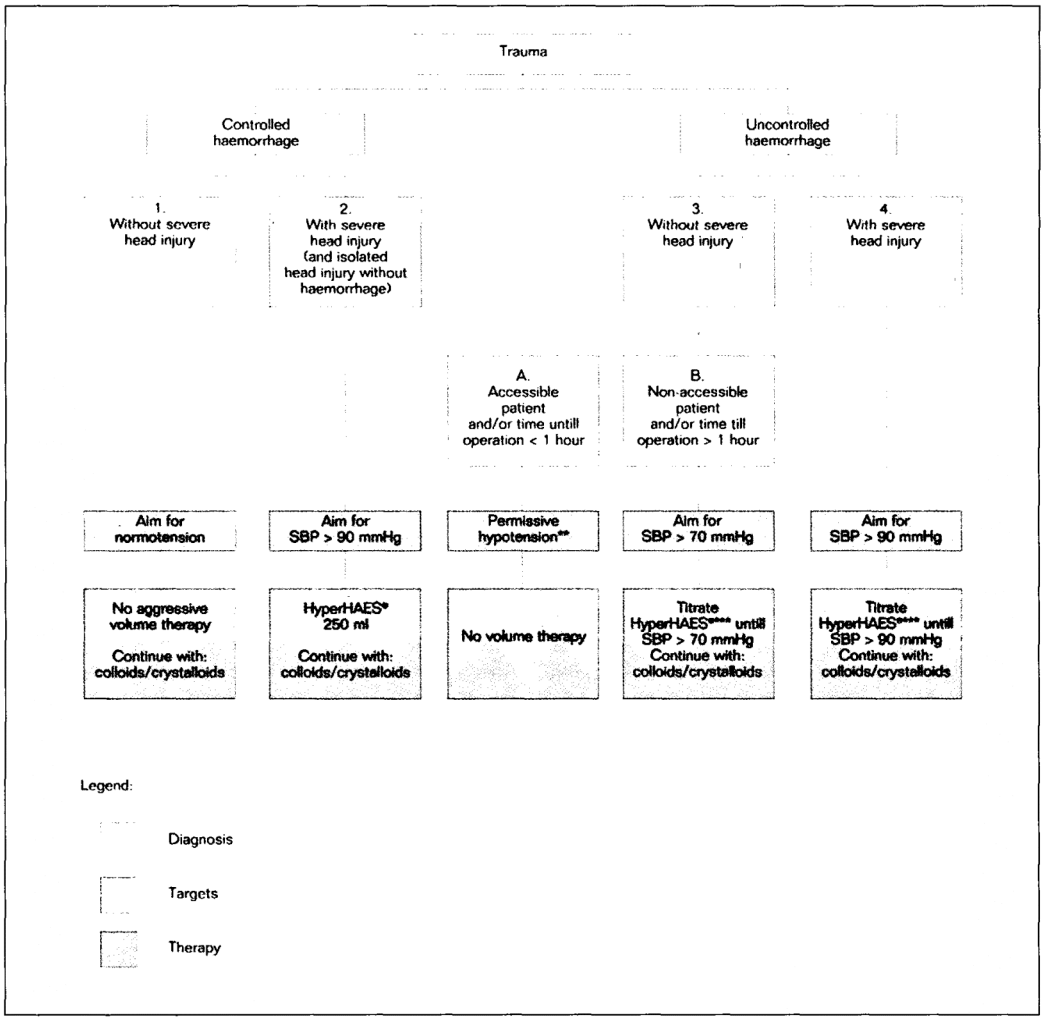

Table 7. Volume therapy in traumatology (guidelines by Van Eijk et al.)[54]

** 'Permissive hypotension' in traumatology is the temporary acceptance of relatively low blood pressure in situations in which haemorrhage is not yet controlled. There are strong indications that permissive hypotension is preferred to normotension.[11,133] It is difficult to find the optimal amount of fluid, but the aim is the smallest volume which achieves the desired effect. In isolated head injury, permissive hypotension is not recommended. In head injury combined with uncontrolled haemorrhage, permissive hypotension is controversial. In this case the members of the working group advise to aim for a SBP (Systolic Blood Pressure) > 90 mmHg.[54]

*** The maximal dose of HyperHAES® is 250 ml (or 4 ml/kg). HyperHAES® - available in bags of 250 ml – is a hypertonic iso-oncotic solution of 6% HES 200/0.5 in 7.2% NaCl.

4. Summary: The *colloideal* plasma replacement strategy ... ?

Defining the ideal volume replacement strategy is a big challenge. The choice between colloid and crystalloid solutions continues to generate controversy. This crystalloid/colloid debate has been complicated by a colloid/colloid debate due to the number of options available.

Previously, mortality has been used predominantly as the measure to assess which volume therapy is to be preferred. New concepts in critical care, such as tissue perfusion and organ function. anti-inflammatory effects, immunological aspects and wound healing may be better determinants for the selection of fluid to be used.

In the summaries below, we provide an assessment of the *colloideality* of the different available colloids. We also wish to mention that in the next issue of CPO Anaesthesia, part II of "Plasma Replacement Strategies", this subject will be discussed further.

Gelatins

Gelatins have a relatively low average molecular weight of around 35 Da, and are retained in the intravascular space for only a limited time period. Overall, gelatins seem to have no adverse effects on kidney function, though case reports of acute renal failure after gelatin infusion have been published.

The capacity of gelatin to release histamine, the theoretical transmission of prions, the high ureum content of urea cross-linked gelatin. and the interference with clot formation exclude gelatin from being an ideal colloid.

Dextrans

There are some old studies and case reports linking dextrans to acute renal failure. Proposed mechanisms are hyperoncotic acute renal failure, tubular obstruction and direct toxicity.

Other serious side effects of dextrans include coagulation abnormalities, and anaphylactic or anaphylactoid reactions. Therefore, the use of dextrans to treat hypovolaemia is not recommended.

Albumin

Albumin IS expensive, and outcome benefit has not been shown in either hypovolaemic or hypoalbuminaemic states. In contrast. in conditions with increased vascular permeability. leakage of albumin into the interstitial compartment can worsen oedema. Albumin cannot be recommended for correction of hypo vol aemi a because of its high cost and superior synthetic alternatives.

Hydroxyethyl starch

Of all colloids, HES is the most intensively studied plasma volume substitute. HES may have distinct clinical benefits over other fluids,72 resulting in better haemodynamic parameters, improved microvascular blood flow and tissue oxygenation compared to albumin. gelatin and crystalloids.

Starches are associated with less allergic reactions than other synthetic colloids. There is much variation between the different starch solutions. Older starch solutions seem to have a negative influence on coagulation and possibly kidney function; this reduces their maximally daily dosage. More modern cornderived HES solutions have fewer or no adverse effects.

An impressive and growing publication list for HES 130/0.4 produced from corn, demonstrates its safe use in numerous clinical scenarios, including paediatrics, impaired kidney function and high dosage. Whether the same is true for potato derived starch solutions remains to : be seen, as much essential information is still unknown.

Taking everything in account, 6% HES 130.4 from corn (maize) seems to be the most colloideal solution for routine use available in Europe. 6% HES 130/0.4 combines a good safety profile with an optimal volume efficacy and reduces requirements of blood products, resulting in a superior cost-effectiveness.

When long-lasting haemodynamic stability is required, and in states of increased vascular permeability, the use of 6% HES 200/0.62 is recommended. Small volume resuscitation with hypertonic starch is beneficial in head injury and in severe hypovolaemic states (haemorrhagic shock, emergency medicine, declamping).