

A collection of military medals and a pair of glasses is displayed on a light-colored surface. On the left, a blue ribbon with a red star-shaped medal is visible. Below it is a larger, ornate silver star-shaped medal with a central emblem. To the right of these medals is a pair of gold-rimmed glasses with thin temples. In the bottom left corner, a circular compass is partially visible. The background is a plain, light-colored surface.

# Plasma Expanders: “Expanding the options”

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# Crystalloid vs Colloids debate

- ◆ Ongoing and many schools of thought.
- ◆ Whichever one chooses:
  1. Choose the fluid for the correct purpose.
  2. Know the composition of the fluid chosen.
  3. Be aware of the risks and benefits of the particular fluid chosen.



# Crystalloids vs Colloids

## Crystalloids:

- ◆ Extracellular space expanders primarily.
- ◆ Net effect is 1/3 to 1/4 of total fluid infused.
- ◆ Intravascular  $t^{1/2}$  can vary down to as little as 20-30 minutes.
- ◆ Limited volume expansion over long term time period.
- ◆ Maintain urine output and renal function in the crucial initial stages of volume resuscitation.
- ◆ Potentially reduce plasma oncotic pressure by diluting plasma proteins, if given in large volumes!
- ◆ Variable electrolyte content.
- ◆ Cost effective and less expensive compared to the colloids.



# COLLOIDS

## **Colloids:**

- ◆ Intravascular space expanders.
- ◆ Volume for volume expansion (varies per individual colloid chosen).
- ◆ Osmotically active with high molecular weights.
- ◆ Maintain oncotic pressure.
- ◆ Coagulation problems.
- ◆ Variable electrolyte content and  $t_{1/2}$ .
- ◆ Intravascular half-life varies from 2-8 hours.
- ◆ Adverse reactions.
- ◆ Costlier than crystalloids.



# INDICATIONS FOR COLLOID THERAPY

1. Fluid resuscitation, especially in severe fluid deficits (eg haemorrhagic shock) prior to blood availability for transfusion.
2. Presence of severe hypoalbuminaemia or diseases of large protein loss e.g. burns.
3. In conjunction with crystalloids if fluid load exceeds 3-4l prior to transfusion.
4. Fluid boluses in critically ill patients, where volume is critical and crystalloids use would be excessive e.g. ICU, Renal, CCF, Pulmonary oedema etc.



## Current available colloid solutions

1. **Albumin**
2. **Dextrans**
3. **Hydroxyethyl starches**
4. **Gelatins – succinylated gelatins & polygelines**
  - ◆ All have their merits and areas of usage clinically.
  - ◆ The **most commonly used 2** are the starches and the gelatins.
  - ◆ In the EU the trend is away from the traditional gelatin towards the hydroxyethyl starches.
  - ◆ Shift from traditional 60/30 split in favour of gelatins over to hydroxyethyl starches.
  - ◆ In the USA, the use of gelatins is far outweighed by the usage of the starches. In fact, they are not even freely available in the USA.
  - ◆ Even though some gelatins are derived from SBE free sources, the recent scare of SBE has potentially negatively impacted on the gelatin usage.



# What is the ideal colloid?

- ◆ One which displays the following in plasma replacement:
  1. **Rapidly replaces blood volume losses.**
  2. **Restores the haemodynamic balance.**
  3. **Normalizes microcirculatory flow.**
  4. **Have a sufficiently long intravascular life.**
  5. **Improves haemorrheology.**
  6. **Be readily metabolized, readily excreted and well tolerated.**
  7. **Be free of side effects, especially regarding haemostasis and anaphylactoid reactions.**
  8. **Be cost effective and contribute to blood savings.**

National Research Council USA (1963)

- ◆ Unfortunately NO colloid fits into all the criteria, all of the time.
- ◆ Idea is to use the best colloid for the patient, to achieve the desired effect with the least amount of side-effects.
- ◆ **Show that the medium molecular hydroxyethyl starches closest fit the above!**



# Albumin

- ◆ One of the **original plasma expanders**.
- ◆ Accounts for 60-80% of normal plasma oncotic pressure.
- ◆ **Derived from pooled human plasma**.
- ◆ Available as Albusol® in 4% & 20% solutions.
- ◆ Albumin levels are mostly used as prognostic indicators, rather than an absolute value to be maintained by exogenous albumin infusions.
- ◆ It is a blood derived product which has its own problems:
  - **availability.**
  - **high cost.**
  - **general scarcity of blood products at a blood bank level.**
  - **theoretical risk of transmission of contagions, although ALL plasma in the pool is tested –ve for HbSAg and HIV.**



◆ **Current indications include:**

1. Severe **hypoalbuminaemia** with clinical manifestations.
2. Immunoglobulin deficiencies.
3. Plasma cholinesterase deficiencies.
4. (The use of a bottle of albumin concurrently with a diuretic to decrease peripheral oedema and improve urine output in patient's with anasarca is under scrutiny).
5. Possible future roles include utilising albumin for its potential **free radical scavenging**.



◆ **Disadvantages:**

1. Studies have shown that albumin administration does not decrease morbidity or mortality in critically ill patients (*Traylor R – Anaesth Analg 1996*).
  2. In fact further studies have gone as far as to claim that it may be associated with an increased mortality of, on average, 6 extra deaths for every 100 patients treated (*Cochrane Injuries Group – Albumin Reviewers, BMJ, 1998*).
  3. Albumin may lead to cardiac decompensation when infused rapidly.
  4. Has been reported to have a partial extravascular distribution, which may accentuate respiratory failure and other organ dysfunction.
  5. It may also be antithrombotic and have harmful renal effects (*Offringa M – Excess mortality after albumin, BMJ, 1998*).
- ◆ Clearly not the colloid of choice for high volume resuscitation, especially in the acute setting.



# Dextrans

- ◆ **Branched-chain polysaccharide.**
- ◆ May produce plasma expansion by a colloidal osmotic effect.
- ◆ Has been mostly used in restoring intravascular volume in the treatment of shock or impending shock as a result of haemorrhage and burns.
- ◆ 2 preparations include:
  - **dextran 70, 6% (Macrodex®)**
  - **dextran 40, 10% (Rheomacrodex®)**
- ◆ Both are in a 0,9% saline solution.
- ◆ 50-70% excreted unchanged in the urine. The rest is metabolised in the liver into water and CO<sub>2</sub>.



◆ **Advantages:**

1. ↓ blood viscosity.
2. ↓ platelet adhesiveness.
3. ↓ RBC aggregation (anti-thrombotic).
4. Improve blood flow through the microcirculation.
5. Also implicated in suppressing excessive platelet-leukocyte-endothelial interaction.


◆ **Clinical advantages and uses include:**

1. Plastic surgery, especially flaps to maintain and assist in perseverance of pedicle vascular integrity.
2. Improve peripheral blood flow in the treatment and prevention of thromboembolic disease associated with surgery.
3. Peripheral vascular disease to improve the microcirculation, especially peri-operatively.
4. Useful in the prevention of excessive platelet activation and release of microemboli during endarterectomy, stent grafting and other vascular procedures.



◆ **Disadvantages:**

1. Much briefer volume expansion effect compared to the starches and gelatins (due to rapid clearance and small MW).
2. One of the highest risk of anaphylaxis amongst all the colloids, including hypersensitivity reactions. Ranges from rash, pruritis and hypotension to full blown anaphylaxis. The rash, pruritis and hypotension are mostly due to its potential antigenicity.
3. Severe risk of bleeding following usage, may prolong bleeding time.
4. Can interfere with blood typing (cross matching and grouping). Always take a blood sample prior to administration of a Dextran.
5. Antiplatelet.
6. Can be associated, or worsen renal failure/compromise.
7. If Heparin is used concurrently, recommendation is to decrease the dosage by 35-70% due to synergistic effect on the coagulation.
8. Watch for and correct any dehydration due to the increase in viscosity of fluid in the renal tubules due to the Dextran.
9. Patient's have to be watched carefully for post-operative bleeding due to the improved microcirculation, especially due to the Dextran 40.

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- ◆ Dextran 1 hapten commercially available:
    - binds with the dextran antibodies.
    - additional cost.
    - Promit® (Dextran 1 in a 0,6% Saline solution).
  - ◆ Total dose in first 24 hours < 20ml/kg and then < 10ml/kg on subsequent days.
  - ◆ Unfortunately, the disadvantages negate its use as a high volume resuscitation option and its use is concentrated in a more niche setting.



# Gelatins

- ◆ Second most commonly used plasma expanders (colloid) after the hydroxyethyl starches.
- ◆ 2 different formulations:
  1. 4% modified (succinylated) fluid gelatin - Gelofusine®
  2. 3,5% polygeline - Haemaccel®. Degraded gelatin polypeptides, cross-linked via urea bridges.
- ◆ The succinylation of the Gelofusin® results in a –ve charge, which supposedly spreads out the molecule. This results in the shape filling the required volume greater than the non-succinylated gelatines of the same molecular weight (Haemaccel®).



- ◆ **Indications:**
- 1. **Prevention and treatment of hypovolaemia:**
  - Following shock due to haemorrhage or trauma.
  - Peri-operative blood loss.
  - Burns.
  - Sepsis.
  - Epidural/spinal anaesthesia.
- 2. **Haemodilution.**
  - ◆ (In essence the same indications as the hydroxyethyl starches, or any colloid).



# Advantages

- ◆ Neither of the two formulations contain any preservatives in their manufacture.
- ◆ The average MW is between 30000 and 35000 daltons.
- ◆ **Rapid excretion from the body via the urine, with complete plasma clearance within 3 days and complete excretion from the body in one week.**
- ◆ Up to 50% removed within the first 4-8 hours following administration.
- ◆ Only about 1% is metabolised of the infused amount.
- ◆ No storage within the RES.
- ◆ They claim to have no effects on coagulation with disturbances, unless due to dilution and ↓ the thrombin levels.



- ◆ The claim on lower effects on coagulation could be due to the rapid clearance and the relatively low molecular weight and size.
- ◆ No specific dosage limitations as per PI.
- ◆ May be some benefit over the hydroxyethyl starches in renal compromised patients due to the rapid clearance (Extrapolation results from a trial comparing renal function in kidney transplant patients after donors received Haesteril + Gelatin and Gelatin alone, *Cittanova M, The Lancet December 1996*).



# Disadvantages of Gelatins

- ◆ They are derived from a bovine source:
  - more than likely from a SBE free source.
  - always a concern where a medical product is sourced from an animal source.
  - the theoretical risk of transmission of a contagion is unfortunately there.
  - the low usage of the Gelatins in the USA.



- ◆ Ultimately, they are volume replacers as opposed to volume expanders:
  - they exhibit rapid migration out of the intravascular space.
  - as a result, one needs more volume to achieve the same volume expansion effect as a hydroxyethyl starch.
  - this raises the issue and possibility of overhydration of the patient, especially if critically ill or renal / cardiac compromised.



- ◆ **Volume effect is 3-4 hours:**
  - lower than the starches which vary from 4-8 hours.
  - as already mentioned, more potential volume required to achieve desired effect.
- ◆ **Claim to have diminished effect on the clotting profile:**
  - however, as with all colloids, clotting abnormalities are stated as a contraindication.



◆ **Anaphylactoid reactions:**

- clinical studies have shown gelatins to have the highest incidence of reactions of all the commercially available colloids.
- Haemaccel® has been linked to potentially fatal histamine induced reactions.
- Reactions can vary from benign skin symptoms (urticaria) and facial flushing down to the more severe and true anaphylactic reactions (hypotension, bronchospasm, shock, cardiac and respiratory arrest).
- The reactions can be both histamine mediated and histamine independent.
- Possible use of H1 & H2 blockers.
- Prophylactic use of corticosteroids have not proven to be of value.



# Hydroxyethyl Starches

- ◆ First developed in the 1960's as an alternative to the traditional plasma expanders at that time viz. Albumin and Dextrans.
- ◆ Have progressed tremendously over the years from their beginnings in the 60's.
- ◆ Started off with very high molecular weight entities and is continually changing and adapting to suit the need for lower weighted fluids, with maximal benefits.



# Available Hydroxyethyl Starches

- ◆ Haesteril® 6% (200/0.5)
- ◆ Haesteril® 10% (200/0.5)
- ◆ Sabax Pentastarch® 6% (200/0.5)
- ◆ Voluven® 6% (130/0.4)
- ◆ Sabax Hetastarch® 6% (450/0.6)



# Hydroxyethyl starches

- ◆ All derived from **amylopectin**, which is chemically modified.
- ◆ Found in **wax corn starch**.
- ◆ Natural, non-synthetic product.
- ◆ Available in **isotonic** solutions.
- ◆ Osmolarity in the 310 mOsm/l range (close to normal physiological osmolarity).
- ◆ Concentration 6% & 10%.
- ◆ Approximate pH 5,5.
- ◆ In a 0,9% Saline solution (9g NaCl & 60g starch)



- ◆ Molecular weights vary from 450 Daltons down to 130 Daltons.
- ◆ Differ in the degree of substitution, as well as the substitution ratio.
- ◆ Vary greatly in the  $t^{1/2}$  intravascularly, duration of effect and plateau effect, as well as the rate of elimination.
- ◆ Costly as compared to crystalloids (as are all plasma expanders).



## 10% Hydroxyethyl Starches, higher molecular weighted starches

- ◆ High molecular weight starches have a very **narrow therapeutic benefit range**.
- ◆ Due to their higher concentration, the **duration of action may be long with a plateau effect which is significant and sustained**.
- ◆ However, their **general use is limited to isolated areas** e.g. cardiac surgery while on bypass.
- ◆ **Trend away from the extremely high MW starches due to undesirable potential side effects.**
- ◆ They are tainted with undesirable incidences of coagulation defects, prolonged stay in the system, overloading and increased anaphylactoid reactions.
- ◆ For this reason, they are not ideal in the acute volume fluid resuscitation scenario.
- ◆ The major use of plasma expanders is in the field of acute volume expansion and maintenance, of which the medium to lower hydroxyethyl starches are the ideal.

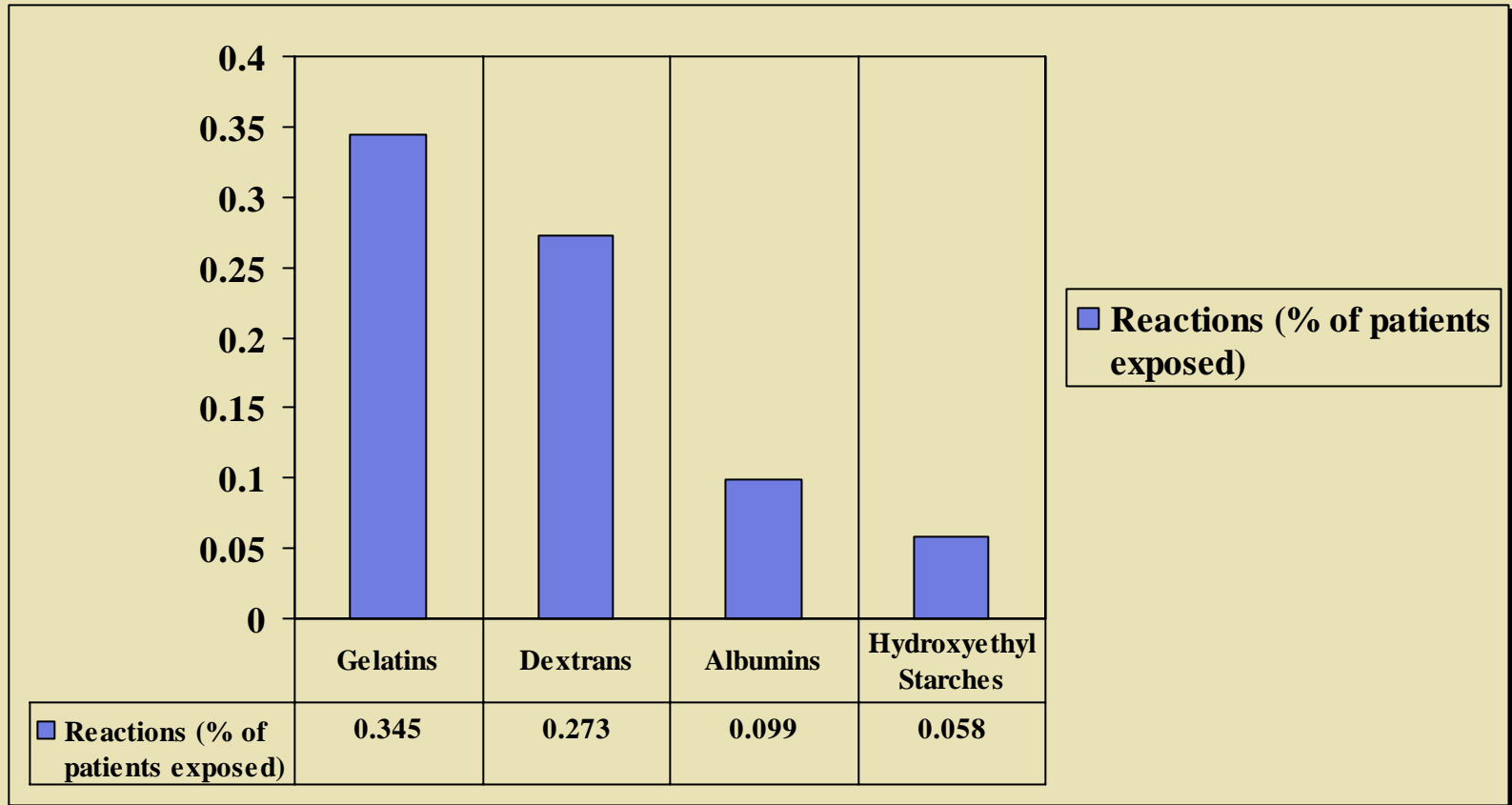


## Benefits of Hydroxyethyl Starches

- ◆ Very good plateau effect of up to 4 hours.
- ◆ Relatively short intravascular half-life of 2-3 hours.
- ◆ Volume efficacy of 1:1 with duration varying from 4-8 hours.
- ◆ Broken down by amylase in the plasma.
- ◆ Essentially removed by:
  1. Renal excretion (particles < 50 after degradation).
  2. Redistribution.
- ◆ Rapid excretion with 70% eliminated within the first 24 hours and >85% after the first 7 days.
- ◆ Extremely low incidence of anaphylaxis reactions compared to other colloids (lowest incidence of reactions amongst ALL colloids)

# Risk of anaphylactoid reactions with colloids


*(Laxenaire MC et al, Ann Fr Anaesth Reanim, 1994)*





# Further benefits

- ◆ They may also decrease the release of vasoactive mediators and beneficially alter membrane stabilization.
- ◆ *Boldt M, Anaesth Analg 1996* showed improved systemic haemodynamics, including improved splanchnic perfusion in both trauma and septic patients.
- ◆ Even with doses of hydroxyethyl starches 200/0.5 larger than recommended, there has not been significant increase in clinical bleeding and organ toxicity.
- ◆ *Vogt N Anaesth Analg 1996* demonstrates the safety of 200/0.5 at doses larger than the recommended (20-36 ml/kg vs. max of 20 ml/kg). This might not be so in critically ill patients or those with renal impairment.



# Potential disadvantages of hydroxyethyl starches

## ◆ Severe pruritis:

- potential problem in LONG-TERM usage of hydroxyethyl starch infusions.
- highly unlikely in the relatively acute setting of volume resuscitation and treatment of hypovolaemia.
- ? Due to formation of intracytoplasmic storage vacuoles in the skin and the Schwann cells of myelinated and unmyelinated small nerve fibres (*Metze D, British Journal of Dermatology April 1997*).
- Reported to respond to topical capsaicin (*Warren B, Anaesthesia and Analgesia, 1997*).

## ◆ Errors in Serum amylase levels:

- some authors report that serum amylase should not be used a marker for diagnosis of pancreatic disease following the infusion of a hydroxyethyl starch ( *Warren B, Anaesthesia and Analgesia, 1997*).



# Hydroxyethyl Starches

- ◆ The volume effect, duration of action and elimination as well as effect on coagulation is dependant on various factors:
  1. Molecular weight size.
  2. Degree of substitution.
  3. Ratio of substitution.



# Molecular weight size

- ◆ The starches vary in size from 450 Daltons down to the medium to low range (200 and 130 Daltons).
- ◆ The molecular weight is responsible for the degree of elimination, as well as the effect on coagulation.
- ◆ **The lower the MW, the less the effect on the coagulation.**
- ◆ Trend is towards the lower the MW.
- ◆ **Much debate between the relative merits of the 200 vs. 130 starches.**



# Degree of substitution

- ◆ Relates to the number hydroxyethyl molecules substituted on the carbon skeleton of the glucose pectin entity.
- ◆ Expressed as a ratio.
- ◆ The number of hydroxyethyl's per number of glucose e.g. 0,5 = 5 hydroxyethyl starches per 10 glucose molecules.
- ◆ **Of what relevance is this?**
- ◆ The higher the degree of substitution, the more the degradation of the starch by serum amylase is resisted.
- ◆ This relates into a longer duration of action and volume effect.
- ◆ By having this delayed breakdown and elimination, sufficient quantities remain in the plasma to effect an effective volume effect with the least amount of colloid infused.
- ◆ Ideally, one can then get a 1:1 volume effect.
- ◆ This compares to gelatins, which due to their more rapid elimination, have a lower duration and volume effect. As a result, one often needs appreciably more volume to maintain the desired volume effect.



# Substitution pattern

- ◆ Worked on a **C2 to C6 ratio**.
- ◆ The relative ratio of the hydroxyethyl starch substitutions at the carbon level.
- ◆ The relevance is related to the **effect on coagulation**.
- ◆ **Studies have shown that the higher the C2/C6 ratio, the increase in the negative effect on coagulation.**
- ◆ Ultimately, all colloids have a possible negative effect on coagulation, be it from:
  1. Direct effect on clotting factors, especially FVIII and VWF.
  2. Direct effects on platelet function and kinetics.
  3. Dilutional effect on coagulation.



# Effects on coagulation

- ◆ Current debate is: do the lower (130 dalton) starches have a lesser effect on coagulation compared to the medium (200 dalton).
- ◆ Even though the 130/0.4 has a lower MW compared to the traditional 200/0.5, there is significant differences in the degree of substitution and pattern to suggest not.
- ◆ In fact the 130/0.4 starches have a higher C2/C6 ratio (11:2) compared to the 5:1 of the 200/0.5 ratio. This we have seen is directly linked to an increased effect on coagulation.
- ◆ *Jamnicki et al, Anaesth Analg, 1998* – states **“130/0.4 has a higher C2/C6 ratio (11:2) than 200/0.4 (5:1). Because a high C2/C6 ratio is associated with an exaggerated blood coagulation compromising effect, it is conceivable that the effects of a lesser mean MW and a higher C2/C6 ratio of 130/0.4 can result in a blood coagulation compromising potency similar to the higher MW but lower C2/C6 ratio of 200/0.5”**



- ◆ *Jamnicky* goes on further to state that “we found no difference in the blood coagulation compromising potency between 130/0.4 and 200/0.5 starches”.
- ◆ *Entholzer EK, Acta Anaesthesiologica Scandinavica, 2000* – “However molecular weight is not the only determining factor of haemostatic side effects caused by hydroxyethyl starches. 130/0.4 has a higher C2/C6 ratio (>8) than the 200/0.5 solution (5:1). Since a high C2/C6 ratio is also related to an increased coagulation compromising potency, this may in fact account for the only slight differences in comparison to 200/0.5”.




# Anaphylactoid reactions

- ◆ As already seen, the incidence of reactions in the Hydroxyethyl Starches is the lowest amongst all the colloids.
- ◆ The hydroxyethyl starches have evolved over the years and the incidence of reactions have decreased.
- ◆ The incidence varies, but currently sits at about **0,058%**.
- ◆ The lower (130/0,4) have made claims of a lower reaction rate compared to the traditional ( 200/0,5).
- ◆ Unfortunately, with no clinical studies to confirm this.



# Platelet properties

- ◆ All colloids have also been implicated in direct effects on platelets.
- ◆ *Franz et al Anaesth Analg, 2001* – “the reason for reduced anti-platelet properties of 130/0,4 is UNCLEAR, but this finding may indicate the degree of substitution is more critical than molecular weight in determining the effect on platelet function” This is a hypothesis and needs more clarification, but based on what we know about C2/C6 ratio, the potential for anti-haemostatic properties is as potent in the lower weighted starches as compared to the medium weighted.
- ◆ *Franz et al* state “fluid resuscitation with 130/0.4 MAY reduce the risk of bleeding associated with higher molecular weights”.
- ◆ Further studies and clarification is required to substantiate the claims with regards to the effect of 130/0.4 hydroxyethyl starches on coagulation.



# Final note on the virtues of the 130/0.4 starches vs. 200/0.5 starches

- ◆ The **French Ministry of Health** did a transparency report on the merits of the newer 130/0.4 starches compared to the older 200/0.5 starches.
- ◆ Criteria include:
  1. Normovolaemic haemodilution
  2. Treatment of hypovolaemic fluid loss, especially secondary to haemorrhage, burns.
  3. The filling efficacy of the two fluids I.e. volume effect.
  4. Effect on the coagulation profile.
- ◆ **Result:**
  - **The newer, lower 130/0.4 molecular weighted starches do not offer an improvement in the medical services rendered as compared to the traditional 200/0.5 hydroxyethyl starches.**

## Composition comparison of available colloids

	Albumin	Dextrans	Gelofusine	Haemaccel	Hydroxyethyl starches
Osmolarity (mOsm/L)	260	350	274	280	308
Ph	7,5	3,5 - 7,0	7,4	7,0	5,5
Solvent	Plasma	Saline 0,9%	Fluid Gelatin	Fluid Gelatin	Saline 0,9%
Na	130	154	154	145	154
Cl	130	154	120	145	154
Ca	1,2	nil	0,4	6,25	nil
K	3,5	nil	nil	5,1	nil
Phosphates, Sulphates	nil	nil	nil	Trace	nil
Molecular weight	69,000	40,000 & 70,000	30,000	35,000	130,000 - 200,000
Maximal recommended dose	2L per 24 hours	< 20ml/kg on first day	<20ml/kg day	500-1000ml	< 20 ml/kg day
		< 10 ml/kg after	Maximum 1000-2000ml	Max 1500ml	Max 1500ml




- ◆ Ultimately, whichever colloid is chosen, they should fulfill the required principles for hypovolaemia:
  1. Normalize blood volume.
  2. Regulate blood pressure.
  3. Stabilize cardiac function.
  4. Improve tissue perfusion.
  5. Raise oxygen delivery.



Why are starches widely considered the best candidates to closely fit the requirements of the “IDEAL COLLOID”?

- ◆ **Highly Cost-effective and Blood saving contributors (vs Albumin).**
- ◆ Due to amylopectin structure, **no safety contamination risks** (human viruses, prions vs Albumin or SBE vs Gelatines).
- ◆ **Starches are the safest colloids** with no Acute Renal Failure (renal & bleeding diathesis vs Dextrans), the lowest anaphylactoid incidence (no immune complex vs Dextrans, nor histamine release vs Gelatines).
- ◆ **Starches offer sustained volume effect duration and better haemodynamic and cardiorespiratory function restoration.**



# How does one choose the right colloid for the job at hand

- ◆ Know the relevant benefits of each colloid available.
- ◆ Give the colloid which achieves the maximal correction for the clinical deficit, with the minimal volume given.
- ◆ Choose the most cost effective colloid for the task, with proven benefits to justify the expense.
- ◆ Ideally choose the colloid with the least clinically proven side effects and complications. Special care with anaphylaxis, coagulation potency and storage.