

One in a series of reports concerning meetings on topics relevant to the clinical use of human serum albumin

Advances in Fluid Resuscitation

Report of presentations made during the 22nd International Symposium on Intensive Care and Emergency Medicine, held in Brussels in March 2002.

Introduction

The International Symposium on Intensive Care and Emergency Medicine (ISICEM) continues to be the major congress in this therapeutic area and each year provides a forum for discussion, education and presentation of research results. The Chairman of the Symposium, Professor Jean-Louis Vincent (Belgium) welcomed delegates to the 22nd ISICEM at the Brussels Congress centre, with numbers of delegates anticipated to exceed 4000, improving yet again on the record of the previous year.



Professor
JL Vincent

Professor Vincent made 'The Great Step Forward' the subject of his opening address. He pointed out that one of the current challenges of intensive care (IC) medicine is that little, other than the improving skills and quality of IC physicians, has been shown to improve outcomes for the ICU patient. Alternatively, a number of management techniques and interventions are not supported by evidence that they are beneficial and, indeed, some have been shown to be detrimental.

Fashions also influence ICU management. For example, the Swan-Ganz catheter is now used less frequently and there is no evidence to indicate whether it is of benefit or otherwise. Some people refuse to give albumin in the ICU, but Professor Vincent said he still did so. The refusals are based on the evidence of the Cochrane Injuries Group's meta-analysis published in the British Medical Journal in 1998 (317, 235). There have been many discussions concerning the methodology of this meta-analysis, to the extent that in a recent issue of the Lancet (2002, 359, 70), Horsey concluded that all the evidence cited by the Cochrane reviewers concerning albumin administration in hypovolaemic patients is flawed and those who have called for the use of albumin to be stopped should retract their demands. Indeed, Wilkes and Navickis have published a meta-analysis showing that the use of albumin did not increase mortality rates in clinical trials (*Ann Intern Med*, 2001, 135, 149). Professor Vincent has collaborated with Drs Wilkes and Navickis and with his colleague Marc-Jacques Dubois on a meta-analysis of the risks associated with hypoalbuminaemia in the acutely ill. The findings were presented in abstract form at the 22nd ISICEM and are summarised on Page 12.

Advances in fluid resuscitation

The question of appropriate fluid resuscitation in the acutely ill remains one of controversy and the ISICEM sessions on intravenous fluids are always well attended.

At this 22nd meeting, in a session moderated by Keith Walley (Canada) and Djillali Annane (France) advances in the use of hypertonic solutions and oxygen carrying solutions were discussed, together with presentations concerning colloid administration.

Hypertonic solutions

Hypertonic saline dextran

In a short history of the development and discussion of some the functional aspects of hypertonic saline dextran solution (HSD), Professor Charles Wade (USA) described how HSD was developed in the early 1980s to try to fulfil US military requirements for a solution that:

- Expanded blood volume and maintained the expansion of blood volume for up to 3 hours
- Remained stable and did not require refrigeration



Professor
Charles Wade

- Could be used in harsh environments with temperatures ranging from -40°F to 120°F
- Had some pharmacological properties

The two options investigated were haemoglobin solutions and crystalloid/colloid therapies. The crystalloid/colloid preparation that held the most promise was HSD (7.5% saline and 6% dextran), which is hypertonic and slightly hyperoncotic. In a case of hypoperfusion with endothelial swelling, exposing cells to a rapid increase in plasma osmolality shrinks the cells, returning them to their normal state and resulting in movement of fluid from the extravascular space and endothelial cells into the vascular compartment.

HSD as volume expansion

Administration of HSD results in a volume expansion of 1.4mL per mL administered, compared with 0.12mL expansion per mL Ringer's lactate solution (RL), 0.6mL per mL dextran and 0.65mL expansion per mL hypertonic saline administered. The expansion achieved with HSD is also sustained, maintaining the superiority over either dextran or saline alone in this respect. These findings were established in normovolaemic subjects; in the presence of hypovolaemia there is a greater return.

Properties of HSD

Effects on blood pressure
In eight randomised control trials in trauma patients, in comparison with standard of care (SOC), there has been a consistent finding of 20-35mmHg elevation of blood pressure per 250mL HSD administered, sustained over time.

Effects on oxygen transport

In surgical patients, HSD has been reported to increase

cardiac output without changes in central venous pressure (CVP) or pulmonary capillary wedge pressure (PCWP) and improved PaO₂ with an overall improvement in oxygen delivery. In the single study in burn patients, there was no change in cardiac output, but patients achieved an equivalent output at a lower filling pressure when the HSD solution was used.

Immune function in shock and sepsis

In animal models exposed to shock or lipopolysaccharide (LPS) to mimic sepsis, resuscitation with RL, isotonic saline or with a colloid had no effect on transpulmonary albumin leak rates, which are indicative of the degree of insult with the model. When HSD was administered, the leak rate returned to zero; the integrity of the endothelial cells appeared to be a major factor. So far, HSD has only been used in the critical setting in the veterinary literature.

Applications of HSD

Surgical patients

HSD has been used in cardiac bypass patients and aortic surgery patients; administering 250mL of HSD at the end of the procedure led to a reduction in total fluid requirements of 800-1200mL. HSD caused an increased diuresis in absence of traumatic injury; surgical patients had an increased diuresis and a pronounced reduction in the positive fluid balance that is normally associated with colloids or crystalloids.

Emergency patients

After stabilisation and control of bleeding in the emergency room (ER), administration of HSD resulted in a 600mL decrease in total fluid requirements for resuscitation.

Trauma patients

Amalgamation of the findings

of randomised clinical trials (RCT) in trauma patients treated with HSD or SOC who were well matched for age, systolic blood pressure (SBP) and pulse rates at the time of enrolment, and TRISS scores compared survival until discharge following administration of 250mL HSD in the field as the initial therapy. Further treatment was with all conventional fluids and interventions as necessary.

- Survival in the HSD group was 82.7% (249 of 301)
- Survival after SOC was 76.2% (230 of 302)
- The Odds Ratio (OR), in favour of HSD, was 1.49 (CI 1.01-2.23)

This 6% absolute difference represents a 25% reduction in mortality.

Therefore, hypertonic saline colloid solution:

- Effectively expands blood volume
- Decreases fluid volume requirements in a variety of situations
- Decreases positive fluid balance in surgical patients
- Improves cardiovascular function and oxygen delivery
- May positively influence immunological function
- Improves survival

Questions remain concerning the endpoints of resuscitation, the type of follow-on fluid that should be used and volume and rate of fluid administration. At the moment it is suggested that a physiological endpoint should be selected, which can be readily assessed and fluid administration titrated to that endpoint, rather than administration of a bolus volume.

From the existing body of literature, HSD is safe and Professor Wade feels that there are new opportunities for this solution in clinical settings other than trauma, the only area where it is currently approved.

Peter Andrews (UK) discussed the possible applications of HSD in the management of acute brain injury. In health, when the blood brain barrier (BBB) is intact,



Peter Andrews

there is no net movement of sodium or proteins across the BBB. With increasing injury to the BBB, first sodium and eventually proteins can leak into the interstitium. In brain trauma patients, with increasing water and solute loads within the brain, oedema and perhaps a haematoma, the volume of intracranial contents increases resulting in an exponential rise in intracranial pressure that occurs after the volumetric compensatory mechanisms, of cerebrospinal fluid and venous blood extrusion, have been exhausted. This initiates worsening brain cell oxygenation, cerebral vasodilatation and raised brain pressure.

The stages of managing brain injury patients are:

- Resuscitation
- Management of low BP, low cerebral perfusion pressure and raised intracranial pressure
- IV fluid maintenance- but there are controversies at every stage, particularly with regard to the relevance of trials that use monitored physiological variables as endpoints, as such intermediate physiological data have little relationship with the endpoint of primary concern to the patient and the patient's family, that is, mortality.

Cochrane Systemic Review Number 002045 concerning management of brain trauma patients has revealed no benefit of hypertonic versus isotonic

crystalloids or of colloids versus crystalloids, but has suggested a trend to benefit when hypertonic crystalloid and colloid are combined.

In the ICU, raised intracranial pressure is one intermediate physiological variable that does have a strong relationship with survival in the traumatic brain injury (TBI) subgroup. Hypertonic solutions that include dextran may have a role in managing both BP and raised intracranial pressure. Dr Andrews cited Charles Wade's subgroup/cohort analysis of hypotensive head injured patients, with data from previous RCT (*J Trauma*, 1997, **42** (Suppl 5), 61) in which all variables and endpoints were defined before initiation of data handling. This showed that patients who received HSD, compared with SOC, had an improved survival until discharge (37.9%, 39 of 103 patients) compared with those who received SOC, (26.9%, 32 of 119, OR >2), but this was not a prospective RCT.

It can be concluded that:

- The processes after head injury are complex and it is unlikely that a single approach would be suitable for all patients.
- A better understanding of the pathophysiology is needed and consensus on the best models, evaluated by rigorous experimental studies.
- Adequately powered prospective RCT are urgently required.

Christer Svensen
The current status and future potential of hypertonic solutions were reviewed by Christer Svensen (USA).



Christer Svensen

Hypertonic solutions have been used in trauma resuscitation in Brazil and some European countries, such as Austria, for a number of years, but published trial evidence is relatively scarce. Despite most of the work on hypertonic solutions being done in the US, the FDA has not approved HSD because improved survival cannot be adequately proven in single trials. However, none of the currently used crystalloid or colloid fluids has gone through randomised clinical trials or regulatory approval showing improved survival. However, delayed crystalloid fluid therapy has been shown to improve survival in an urban trauma setting (Bickell *et al*, *N Engl J Med*, 1994, **331**, 1105). Conventional fluids are mainly used because they have volume-expanding properties.

Meta-analysis of results from RCT of HSD, treating 1233 patients have shown that there are no safety concerns (Wade *et al*, *Surgery*, 1997, **122**, 609). Evaluating the mean survival until discharge, there was a trend to better survival in the HSD group, compared with SOC.. There was also a significant improvement in survival for patients with head trauma and patients requiring surgery. Subsequently, Wade *et al* (*Acta Anaesthesiol Scand*, 1997, **110**, Suppl., 77) performed a meta-analysis using individual data from six of the eight studies of HSD that showed a significantly lower mortality in patients for whom HSD was infused as the first fluid, in comparison with isotonic therapy.

HSD (as RescueFlow ®) has been registered in Sweden since 1998 and is currently registered in 14 other countries. A hypertonic solution in combination with starches was registered in Germany in 2000. Data from Sweden, where Dr Svensen has been involved with writing the

protocols for use of HSD, has accumulated from urban areas and from a rural area in Lapland; HSD has been distributed to helicopters, ground transport vehicles, ER and ICU. The target patients, mainly traffic accident victims, were those with head trauma, with a Glasgow Coma Score of less than 8 and/or severe shock. Bolus administration of 250mL HSD over 5-10 minutes at the accident scene has improved initial SBP from around 80mm Hg to around 120mmHg at the time of admission to hospital. Patient treatment in Lapland inevitably involved a long transport time to hospital. The helicopter doctors were quoted as reporting that circulation rapidly improved and stayed improved for a considerable time, in spite of sedation, analgesics and positive pressure ventilation. Although there are concerns about re-bleeding if the BP is raised, this has not been seen clinically.

Future uses for hypertonic solutions

- Neurotrauma is one of the areas where patients should benefit most from HSD.
- In sepsis, there are a number of theoretical considerations that would favour the use of HSD rather than crystalloids:
 - Crystalloids, for example RL, are inflammatory - neutrophils are released from the endothelium; hypertonic solutions have been shown to down regulate the inflammatory response
 - T cells are stimulated by hypertonicity
 - Dextran inhibit "leucocyte sticking"

During discussion Dr Svensen pointed out that it has always been the intention to use hypertonic solutions, especially HSD, as the initial fluid. When the initial treatment with

hypertonic solution has been started, there is a requirement to follow up with conventional therapy and give crystalloids or colloids as needed. There are concerns about rebleeding in the trauma scenario if blood pressure is raised too fast and too early, but the risk seems much lower than with anaesthetised research animals in bleeding studies. Concerns about other side effects like hyperosmolarity, hypernatraemia and anaphylaxis from dextran seem to be unfounded. There were no such side effects in the randomised clinical trials.

Ringer's ethyl pyruvate solutions

Mitchell Fink (USA)



Mitchell Fink

It has been known since about 1900 that pyruvate is an effective anti-oxidant, but is unstable in aqueous solution, forming a number of addition and cyclisation products some of which are toxic. Because of some fortuitous observations it was suggested that ethyl pyruvate, a simple derivative, might address some of the some stability issues. This has proven to be so and the compound has also been found to be considerably more active *in vivo* with respect to its anti-oxidant properties, and to have potent anti-inflammatory properties. The compound is already available as food additive and is on the FDA list as generally regarded as safe substance.

Properties of ethyl pyruvate solutions

In animal models of ischaemia and reperfusion injury, Ringer's ethyl pyruvate solution (REPS) preserved virtually normal ileal mucosal architecture, compared with RL. In a model of haemorrhagic shock, oxidant stress in the liver was ameliorated by

REPS resuscitation compared with resuscitation with shed blood plus RL. REPS has also improved survival in a murine model of haemorrhagic shock. These studies from Professor Fink's laboratory are in press.

Anti-inflammatory effects

Anti-inflammatory properties of REPS have been suggested by findings of decreased expression of a number of pro-inflammatory mediators in the liver after resuscitation from haemorrhagic shock, compared with that seen in animals resuscitated with RL.

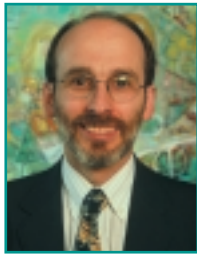
The cytokine of current interest is high mobility group 1 protein (HMG-1) (*Wang et al, Science, 1999, 285, 248*), a late-acting cytokine in sepsis and endotoxaemia, which is seen at 12-20 hours after the onset of the inflammatory process. In patients with sepsis, HMG-1 levels in non-survivors are elevated relative to those in survivors and especially compared to normal controls. In a murine model of endotoxaemia, REPS, in comparison with saline, prevented release of HMG-1, detectable in the plasma 24 hours after challenge. In endotoxin-challenged animals, treatment with five doses of REPS from 4 hours post-challenge converted an LD₅₀ endotoxin dose into an LD₀ dose. Therefore:

- Ethyl pyruvate is a novel agent that has potent reactive oxygen species-scavenging and anti-inflammatory properties.
- Ethyl pyruvate improves survival and / or decreases organ system dysfunction in numerous animal models of shock and sepsis.
- Ethyl pyruvate warrants further evaluation as a therapeutic agent for treatment of critical illness in patients.

Oxygen-carrying solutions

Haemoglobin-based oxygen carriers

As David Mazer (Canada) described, haemoglobin (Hb) solutions have been suggested as an alternative to blood transfusions for



David Mazer

many years, but only in the last 10-20 years have there been significant developments in linking of Hb molecules and stabilisation techniques that avoid many of the problems associated with earlier solutions. Among the haemoglobin-based oxygen carrier (HBOC) products under current or recent development, several manufacturers have used human sources of Hb, one has used bovine Hb and a recombinant form is also under research. The solutions are generally in the 10g/dL concentration range and each manufacturer has its own technique for cross-linking and/or polymerising the products. Half-lives of these products are shorter than red blood cells, the longest being about one day, with the solutions differing in the way that they carry oxygen. There are anecdotal reports of effectiveness, but more controlled clinical trials are required to establish the benefit and safety of these solutions.

Controlled clinical studies

Many of the products are in or have undergone Phase II or Phase III trials. A Phase II dose escalation trial compared Hb raffimer with pentastarch prior to onset of cardiopulmonary bypass (CPB) in combination with intra-operative autologous donation. With 30 patients in each group, four required transfusion with allogeneic blood in the Hb raffimer group compared with 17 in the penta-

starch group. Hb raffimer patients required an average of one unit of blood, compared with about two units in pentastarch-treated patients

In a Phase III double-blind RCT, Hb raffimer was compared with pentastarch for coronary artery bypass graft (CABG) patients; 300 patients were treated at 25 centres and received Hb raffimer or pentastarch 750mL in combination with intra-operative autologous donation (IAD) to a target Hb of 7g/dL. The primary outcome measure was transfusion avoidance. The incidence of allogeneic transfusion was lower in Hb raffimer group, but this did not reach statistical significance. A post hoc analysis was done, comprising patients in whom efficacy was evaluable, rather than an intention-to-treat analysis. This showed a significant reduction in the Hb raffimer treated group in terms of incidence of transfusion avoidance, but has the drawbacks of a post hoc analysis. This company has filed for approval in the UK and Canada.

Biopure's bovine product (HBOC 201) has been evaluated in four significant clinical trials, in cardiac surgery, vascular and general and orthopaedic surgery. Transfusion avoidance ranged from 27% in vascular surgery to 59% in a large trial, according to the company press release. This product is approved in South Africa for peri-operative use.

Diaspirin cross-linked haemoglobin (DCLHb) has also previously been evaluated in cardiac and non-cardiac surgical settings. In a cardiac surgery study, when patients met a transfusion trigger they were either given allogeneic blood or DCLHb. Patients were followed up to seven days post-operatively. The initial benefits seen with respect to allogeneic

transfusion avoidance were not sustained to seven days post-bypass. The problems encountered in the DCLHb trauma trial (Sloan *et al*, *JAMA*, 1999, **282**, 1857) are well known. The higher mortality in the DCLHb group was probably not a problem with this product in particular or HBOC solutions in general, but more likely related to the design, randomisation and/or conduct of the trial.

An evaluation of the safety of HBOC solutions with respect to adverse events in cardiac surgery is summarised in Box 1.

- No difference in mortality between HBOC solution-treated patients and controls
- Higher incidence of elevated blood pressure with HBOC solutions
- Higher incidence of jaundice in HBOC solution-treated patients (expected)
- Slightly higher incidence of abnormal liver function tests with HBOC solutions
- Amylaseaemia (transient)
- No significant alteration of renal function
- Differences in percentage increases in mean arterial pressure (MAP). The greatest differences were associated with DCLHb, and may be related to nitric oxide, volume effects, or endothelin.

Box 1 Evaluation of the safety of HBOC solutions with respect to adverse events in cardiac surgery

Clinical trials with HBOC solutions so far show that:

- HBOC solutions are only one of several strategies that can be used to reduce allogeneic transfusion
- Clinical experience to date in CABG and non-CABG surgery suggests these solutions can
 - Reduce allogeneic transfusion

- Maintain and augment oxygen delivery
 - Data on the safety profile are increasing
 - The role in the trauma patient is not yet known
- It is possible that these solutions will be clinically available in the near future.

Perfluorocarbon emulsions

Donat Spahn (Switzerland) Perflubron, as an artificial oxygen carrier, was first described some 35 years ago.



Donat Spahn

The compound has now been commercially developed for clinical use, after overcoming the difficulties of emulsification for intravenous administration. The droplet size in the emulsion is now stable and biocompatible. There is a linear relationship between PO₂ and amount of oxygen dissolved. (Spahn *et al*, *Critical Care*, 1993, **3**, R93). In order to offload the same amount of oxygen as does blood, the PO₂ must be increased, and administration of perflubron emulsions is usually combined with pure oxygen ventilation.

Clinical studies

In a late Phase II multicentre study in six European countries, including 147 patients undergoing elective orthopaedic surgery, monitoring by was by pulmonary artery (PA) catheter with pre-defined transfusion triggers. The endpoints were the rate and duration of transfusion trigger reversal. The protocol consisted of:

- Haemodilution to Hb 9g/dL (baseline value taken as that post haemodilution)
- First transfusion trigger - surgical bleeding, with
- Randomisation to receive:
 - 450mL autologous blood plus FiO₂ 0.4, or,

	Colloid	Perflubron 0.9g/kg	Perflubron 1.8 g/kg	Autologous blood
Transfusion trigger (TT) reversal (%)	76	82	97*†	60
Duration of TT reversal (min)	30 (27-60)	59† (40-90)	80*† (60-100)	55 (30-70)
Censored observations (%)	13†	45	53	26‡

*, p<0.05 versus autologous blood; †, p<0.05 versus colloid; ‡, p<0.05 versus perflubron 1.8 g/kg

- 0.9g/kg perflubron + additional 450mL colloid + FiO₂ =1.0, or
- 1.8g/kg perflubron + additional 450mL colloid + FiO₂ =1.0, or
- 450mL colloid + FiO₂=1.0

- If the second transfusion trigger reached - blood given.

Best trigger reversal was achieved in the perflubron 1.8 group, which was superior to autologous blood and colloid (Table 1).

A Phase III, prospective randomised study of perflubron emulsion involved 492 patients undergoing non-cardiac surgery at 34 centres. The patients, were scheduled to undergo elective surgery, chiefly major tumour surgery, and had an expected blood loss (EBL) greater than 20mL/kg. The experimental group received:

- Pre-operative normovolaemic haemodilution to Hb 8.0g/dL
- Administration of perflubron emulsion 1.8g/kg at skin incision
- Administration of perflubron emulsion 0.9g/kg at Hb <6.5g/dL
- Autologous blood re-infusion at Hb<5.5g/dl

The control group received:

- Post-operative transfusion trigger: Hb <8.5g/dL
- Allogeneic blood transfusion at <8.0g/dL
- Post-operative transfusion trigger: Hb <8.5g/dL

Table 1 Transfusion trigger reversal in patients undergoing cardiac surgery (Spahn *et al*, *Anesthesiology*, 1999, **91**, 1195).

So far, safety data have not been formally presented (Spahn *et al* and the Oxygent Study Group, *Eur J Anaesthesiol*, 2001, **18** (Suppl. 21, A-204). On an intention-to-treat (ITT) basis, the median number of allogeneic and pre-donated units used was lower in the study group than in controls (0 and 1, respectively), as it was in the subset of patients who fulfilled the criterion of the target population and did, in fact, lose more than 20mL/kg blood during the procedure (1 and 3, respectively). The difference was statistically significant in both analyses. A post hoc analysis showed that the cut off for benefit from the experimental procedure, using perflubron, was around 10mL/kg blood loss, which approximates to 700-800mL in the normal patient. In terms of complete avoidance of blood transfusion, there was a trend to benefit in the experimental group (ITT analysis) at 24 hours. In patients whose blood loss was 20mL/kg, 16% of experimental group patients avoided allogeneic or predonated autologous blood transfusion, compared with 37% of control patients, a difference that remained highly statistically significant until the day of discharge.

Therefore perflubron emulsion, as an artificial oxygen carrier, in particular in combination with pre-operative haemodilution is a valid management option and it is hoped that a Phase III trial can proceed to gain market approval.

Fluid therapy in burn patients

Bala Venkatesh (Australia) With improvements in management techniques, most patients survive the early resuscitation period after a



Bala Venkatesh

major burn, but then some patients continue to be hypotensive and oliguric suggesting intravascular hypovolaemia and others have gross systemic and pulmonary oedema suggesting fluid overload. This raises questions concerning adequacy of fluid resuscitation, what fluids should be given, for how long and to what endpoints.

The most widely used formula to guide fluid supplementation (Parklands formula), suggests administration of only crystalloid in the first 24 hours, with half the calculated volume given in the first eight hours and the remaining half in the next 16 hours. The approach for the second 24 hours it is more debatable, but the Parklands formula suggests introduction of colloids. This formula is simple, low cost, safe, can be used in a community hospital and is appropriate for patients with major burns.

Although under resuscitation is rarely a problem, the consequences are severe and include:

- Early acute renal failure
- Extension of burn
- Lactic acidosis
- Death

The current problem is more one of over-resuscitation, particularly the occurrence of abdominal compartment syndrome, a consequence of excess resuscitation. In this situation, patients have gross ascites, with a rise in intra-abdominal pressure and a decrease in pulmonary compliance. This is more likely to develop when the administered fluid volume for resuscitation exceeds 25% of body weight. Treatment modalities for this syndrome include early recognition, cessation of crystalloids, use of hypertonic solutions to minimize oedema and fluid intake, and laparotomy.

Controversies in resuscitation of the burn patient

Use of colloids

The rationale for colloid use, and the attendant concerns are summarised in Box 2.

Rationale	Concerns
Microvascular leak Hypoproteinaemia Burn oedema Decrease in burn oedema and non-burn oedema	Worsening oedema Increased lung water Coagulation issues Controversial Cochrane Group meta-analysis

Box 2 The rationale for colloid use, and concerns regarding colloid use.

Endpoints of resuscitation

There is controversy concerning appropriate endpoints for evaluating resuscitation (Box 3).

Clinical	Laboratory
MAP Urine output Vital signs CVP	Arterial blood gases Serum Na < 155mmol/L Lactate Haematocrit

Box 3 Currently suggested endpoints for assessment of fluid resuscitation

The current interest is in goal-directed therapy, to hyperdynamic resuscitation and to tissue oxygenation as an endpoint. Schiller *et al* (*J Burn Care Rehab*, 1997, **18**, 10) suggested that hyperdynamic resuscitation improves survival

in patients with life-threatening burns. However, this prospective study with retrospective controls is the only study with this conclusion. There is no prospective RCT evidence. Dr Venkatesh and his colleagues examined tissue oxygenation (*J Trauma*, 2001, **50**, 485) and the CO₂ gap as endpoints during resuscitation of patients with major burns. They concluded that these endpoints did not reflect the adequacy of resuscitation, but reflected local perturbations of oxygen diffusion.

Hypertonic fluids

Hypertonic fluids are normally considered suitable only for initial resuscitation (see Page 3).

Advantages	Limitations
Smaller volume load Reduction in systemic and pulmonary oedema Substantial evidence base	Renal failure Greater mortality Alkalosis (hypertonic lactated fluid) Acidosis (hypertonic saline based fluid) Need for frequent biochemistry

Box 4 Advantages and perceived limitations of hypertonic fluids for resuscitation of burns patients.

With regard to the limitations of hypertonic fluids, an increased incidence of renal failure and higher mortality was reported in one study that retrospectively compared three different time periods with no standard, prospective, clinical endpoints. Alkalosis is not related to the tonicity of the fluid. The study in which alkalosis was reported used hypertonic lactated solution; after administration, lactate will be metabolised to bicarbonate, resulting in a metabolic acidosis. There are no RCT from which to formulate guidelines.

Dr Venkatesh concluded that:

- There is no ideal resuscitation formula for treating major burns
- An understanding of pathophysiology is necessary
- Over-resuscitation is more

- often a problem than inadequate fluid volume
- There is a role for colloids in severely burned patients
- There may be a place for hypertonic fluids
- Conventional clinical endpoints are more useful than other indices

In response to a question, Dr Venkatesh said he thought that the observed increase in incidence of abdominal compartment syndrome may be related to the decreasing use of colloids, particularly albumin, in the early period. This reduction in albumin use has been as a consequence of the publication of the Cochrane Injuries Group meta-analysis.

Colloids

Colloids may improve tissue oxygenation

Joachim Boldt (Germany) Of the complex processes that occur in the ICU patient, one of the most fundamental is the imbalance between oxygen delivery and oxygen consumption (Box 5).



Joachim Boldt

In sepsis, changes of microcirculation occur as a result of:

- Disseminated intravascular coagulation
- Oedema
- Alterations of flow volume
- Endothelial dysfunction
- Abnormal adrenergic reactions
- Increased resistance
- Increased permeability
- Reduced red cell deformability

The question arises of whether the microcirculation can be improved by using volume replacement strategies.

Oxygen delivery is reduced

as a result of
Hypovolaemia
Hypotension
Hypoxaemia
Anaemia

Oxygen consumption is increased by

Trauma
Infection
Endotoxaemia

The combination results in

Tissue hypoperfusion,
Insufficient oxygen delivery
Mitochondrial dysfunction
Cell swelling and damage, and
eventually

Multiple organ failure

Box 5 Consequences of imbalance of oxygen delivery and consumption

Animal studies

The conclusions of animal studies examining microcirculatory blood flow in muscle, liver, kidney and gastrointestinal tract have found:

- Progressive formation of tissue oedema with RL
- Decreased capillary recruitment with crystalloid
- Hindrance of capillary perfusion after crystalloid therapy
- Maintenance of adequate tissue oxygenation by synthetic colloids

Clinical studies

A study of patients undergoing elective surgical procedures measured the rheological effects of plasma substitutes used for pre-operative haemodilution (Audibert *et al*, *Anesth Analg*, 1994, **78**, 740). The study compared 4% albumin, 3.5% dextran 40, 3% gelatin and 6% HES 200/05, measuring plasma and blood viscosity. The conclusions were that:

- Plasma viscosity decreased with albumin and increased with HES.
- Whole blood viscosity decreased with all plasma substitutes and was most pronounced with the starches.

There have been studies of colloids versus crystalloids with respect to tissue oxygen tension in patients undergoing major abdominal surgery. Forty-two patients undergoing major abdominal surgery received volume therapy with 6% HES 130/0.4 or RL solution. Recipients of HES required around 50% less total fluid volume, blood loss was similar in both groups and it could be concluded that tissue oxygenation is improved by using 6% HES 130/0.4.

In septic patients and in acute normovolaemic haemodilution patients, colloids resulted in improved oxygenation while crystalloid-based therapy adversely affected microperfusion and microoxygenation. These studies have been made in skeletal muscles; more important for the patients, but very hard to measure, is the oxygenation of tissues such as the heart, brain or GI tract. There is evidence that splanchnic perfusion may be improved by giving starches rather than gelatins or albumin.

There is a need to improve patients' microcirculatory blood flow and the micro-oxygenation in the organ systems and it would be better if this could be achieved by prevention, rather than treatment of an existing problem. For this purpose, volume therapy seems to be most promising approach, with maintenance of adequate tissue oxygenation, by colloids, involving the possible mechanisms of:

- Decreased whole blood viscosity
- Less interstitial oedema and endothelial swelling
- Improved microcirculation resulting in improved micro-oxygenation

A questioner asked why there were no clinical results to support these hypotheses. Dr

Boldt replied that there are, as yet, no instruments to perform the necessary routine measurements several times a day. The clinical endpoints are not well defined.

Professor Lambert Thijs (Netherlands) gave an overview some of the properties of the principle synthetic colloids. There is evidence from



Lambert Thijs

animal studies that HES compounds with a molecular weight in the range of 200-300 kDa produce less oedema, influence the endothelial linings of the lung in peritonitis models and reduce lung permeability in endotoxin challenge models.

It is difficult to find clinical studies that directly compare colloids. Animal work indicates that dextrans and human albumin reduced the capillary filtration coefficient; when the infusion rate of colloids was increased, HES had no effect and gelatins increased the capillary filtration rate. When volumes of the muscles are considered, indicating capillary fluid exchange, it can be seen that there is less oedema initially with HES but then no difference, but albumin definitely reduces oedema and with other fluids there is an increase.

Among the few clinical studies, HES was compared with gelatin resuscitation in trauma patients, with urine albumin excretion monitored as a measure of capillary permeability. This excretion was significantly lower with HES at two time points than with the gelatin solution, suggesting this type of solution could alter the vessel wall and the endothelial surface. HES (6%, 200kDa, 0.60-

0.66 substitution) was compared with gelatin in a multicentre RCT (Schortgen *et al*, *Lancet*, 2001, **397**, 911). Despite parity at baseline, serum creatinine was significantly higher in the HES group than in the gelatin group at two time points and, overall, patients in the gelatin group did better than the HES-treated patients. There was no significant difference in survival. *In vitro* studies of blood taken from volunteers and diluted with increasing amounts of various fluids - RL, normal saline, albumin 5%, albumin 25% - have examined activation of neutrophils by a luminescence method. RL or normal saline increased the activation of neutrophils. This was not seen with albumin solutions and the expression of CD18 (an adhesion molecule) on neutrophils increased with dextrans and HES. Dr Boldt's group compared 10% HES (mean molecular weight, 200KDa) with albumin 20% and found a reduction in soluble adhesion molecules (sELAM-1, sICAM-1) in those who received HES solution, but these continued to increase in albumin recipients (*Anaesthesia*, 1996, **51**, 529). One explanation could be that HES has a better effect on the microcirculation.

The data are interesting but fragmentary and from many sources and, because there is little patient data, the clinical relevance is still obscure. Professor Thijs said that he was convinced that, in the future and utilising the different properties of these solutions, it would be possible to have specific solutions for specific conditions or specific diseases.

Antioxidant effects of albumin

James Russell (Canada)

For many years albumin has been thought of a simple fluid for volume expansion that has the added effect of being colloid; this may be important in relation to Starlings Law, which concerns colloid osmotic forces in regulating intravascular versus interstitial fluid balance. For the last five to ten years it has also been suggested that there are important non-volume effects of albumin that may have potential clinical relevance, but this is not yet known. The list would include:



James Russell

- Anti-inflammatory effects - in relation to cytokines
- Transition-metal (iron) binding
- Free radical scavenging / anti-oxidant
- Protection against organ (for example, hepatic) injury
- No neutrophil activation / adhesion

The information that provides the background to these proposals tends to be in journals that most clinical intensivists rarely read and concerns the chemistry of albumin *in vitro* and in animal models.

Anti-inflammatory and anti-cytokine effects of albumin

Albumin haemodialysis increased the clearance of TNF α (by 81%) and interleukin (IL)-6 (by 77%) compared to crystalloid dialysis (Awad *et al*, *ASAIO Journal*, 1999, **45**, 47) in an *in vitro* model.

Anti-oxidant activity of albumin

Plasma thiol levels correlate with survival in ARDS. The exposed thiol moiety of albumin acts as an anti-oxidant and,

albumin (20%) infusion in septic patients increases plasma thiols; these increased thiol levels persist even after plasma albumin levels decline (Quinlan *et al*, *Clin Sci*, 1998, **95**, 459).

Animal models also showed that albumin protects against ischaemia / reperfusion hypoxic hepatic injury (Strubert *et al*, *Pharm Tox*, 1994, **75**, 280) and also protects against increased endothelial permeability to macromolecules (Lum *et al*, *Micro Res*, 1991, **42**, 91).

The list is extensive, but the clinical relevance requires investigation. Dr Russell has focussed on a model of the inflammatory response in humans, particularly the model of excessive vasodilation after cardiac surgery, defined as systemic inflammatory response syndrome (SIRS) plus a low systemic vascular resistance index (SVRI). This occurs in up to 44% of patients who have routine elective CPB and there are many papers that have examined the mechanisms, including those involving cytokines (TNF α , IL-1 IL-6), endotoxin and complement.

Dr Russell has started a study to test the hypothesis that 5% albumin, compared to 10% pentastarch, decreases the inflammatory response measured as SIRS plus low SVRI (vasodilatory syndrome). This is in patients having elective, first-time valve and valve replacement surgery, with CABG performed under cardiopulmonary bypass, who will have a PA catheter placed for clinical purposes. Measurements will include pre-operative and post-operative TNF α , IL-1 and IL-6 levels, haemodynamics, Brussels organ function, aPTT, Factor VIII and troponin. Dr Russell had announced that this trial was in planning at the 21st ISICEM in 2001 and it is now underway. An interim analysis has revealed some intriguing

differences between the groups with respect to the vasodilatory syndrome, but the number of patients enrolled so far is too small to allow any conclusions at this time. Another study in pure CABG patients is also in progress.

Does albumin administration worsen outcome?

A number of speakers at this IV fluids session and other speakers during the course of the Symposium, including Professor Vincent, mentioned the meta-analyses that have considered patient outcomes after albumin administration compared with those after crystalloid administration. Mahlon Wilkes (USA) has recently published a meta-analysis of albumin studies with his colleague Roberta Navickis (*Ann Intern Med*, 2001, **135**, 149), discussing mortality after albumin administration in the acutely ill.

The 2001 meta-analysis focussed on randomised trials of albumin versus crystalloid, no albumin or lower dose albumin. There were no restrictions on the types of clinical indications nor were any particular exclusion criteria imposed. This analysis included all trial included in the Cochrane Group's meta-analysis plus additional trials. There was no detectable significant overall effect of albumin on mortality, relative risk (RR) was 1.1, but with a confidence interval (CI) of 0.95-1.27. In some indications the RR was above and in some it was below unity, but in no case was there a statistically significant difference within any of the six categories of clinical indications addressed (surgery or trauma, burns, hypoalbuminaemia, high-risk neonates, ascites, other). These are overall results that include the contribution of trials of poorer quality.

Further investigation showed that trial quality made a substantial difference to the findings of the meta-analysis. Higher quality trials are:

- blinded,
- have mortality as an endpoint,
- have no crossover, or
- include more than 100 patients.

Mortality endpoint

Trials designed to assess mortality as an endpoint rather than physiological variables are more likely to have an adequate follow up period and safeguards to avoid detection bias. Peter Horsey, in his 'Viewpoint' article in the *Lancet* (2002, 359, 70) discussing the randomised trial of Lucas *et al* (*J Trauma*, 1978, 18, 564), noted that the follow up period during which deaths would have been observed was twice as long with albumin group than in controls. This would have the obvious potential to inflate the mortality in the albumin group. In that trial the RR with regard to albumin was twice as high as in any other randomised trial.

Crossover

It was the practice in some trials of attempting to rescue the control group patients by switching them to albumin if their clinical condition deteriorated. On an ITT analysis, the switched patients would retain their control group assignment and the net effect would be to spuriously reduce the apparent mortality rate in the control group.

Large trials

Larger studies are usually recognised to be more rigorously designed and conducted and, overall, more reliable. When these higher-quality trials are examined, they show a potential survival benefit with albumin (Table 2).

Quality attribute	n trials analysed	Relative risk (CI)*
Blinded	7	0.73 (0.48-1.12)
Mortality as endpoint	18	0.99 (0.83-1.17)
No crossover	36	1.03 (0.88-1.21)
100 or more patients	10	0.94 (0.77-1.14)

Table 2 Relative risk associated with albumin administration in trial having one attribute of higher quality. *, Value <1 favours albumin.

If the highest quality trials, defined by having two or more attributes of higher quality, are considered, with respect to all subsets of highest quality trials, the RR was substantially below 1 in favour of albumin (Figure 1).

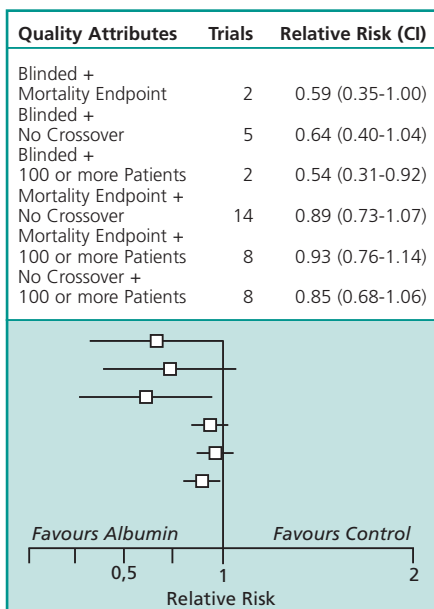


Figure 1 Relative risk associated with albumin administration - meta-analysis of higher quality trials.

Morbidity is also a clinically relevant endpoint and a more sensitive endpoint than mortality. There has been only a single randomised trial showing a significant between-group difference with respect to mortality between albumin and control, but there have been 17 trials concerning morbidity (Table 3).

Endpoint	Total	Albumin superior
Mortality	1	1
Morbidity	17	16*

Table 3 Randomised clinical trials showing significant within-study difference between albumin and control. * In the exceptional study (Lucas et al), the excess morbidity has been recognised as being more related to fluid overload than albumin per se.

Within-study results provide a strong signal, but can the postulated albumin morbidity benefit be confirmed by systematic review and meta-analysis? A further meta-analysis on this topic has been conducted, but has not yet been submitted for publication. Focussing again on the same spectrum of randomised clinical trials, there were 56 with morbidity data, and morbidity was significantly lower in the albumin than in the control group. This significant morbidity benefit persists across four of the five subsets of trials defined by higher quality.

Wilkes and Navickis have also collaborated with Professor Vincent and Marc-Jacques Dubois; their analysis has been submitted for publication and was presented in poster form at the 22nd ISICEM (Navickis *et al*, *Crit Care*, 2002, **6** (Suppl 1, S79, Abst. P171, see Page 12). This study has taken as its focus controlled trials of albumin therapy conducted to correct hypoalbuminaemia and the analysis considered the effect of albumin dosage. At higher doses of albumin, reflected by higher attained levels of serum albumin, the morbidity benefit becomes progressively stronger.

This accounts for 88% of between-study variance, indicating that the dose effect is the predominant determinant of morbidity in these trials.

It can be concluded that there is no overall effect of albumin on survival based on the large, recent meta-analysis, but higher quality trials suggest survival benefit and, based on extensive evidence, albumin appears to reduce morbidity.

Bleeding after cardiac surgery - albumin in comparison with HES

It is known that coagulopathy can cause bleeding after cardiopulmonary bypass surgery and that fluid management may modify the risk. Albumin and HES are used commonly for peri-operative fluid management in CPB patients. Wilkes and Navickis in collaboration with Professor William Sibbald have published a meta-analysis in the *Annals of Thoracic Surgery* (2001, **72**, 527) concerning post-operative bleeding in 16 randomised trials (14 adult, two paediatric) in which a total of 653 CPB patients were treated. HES was delivered at below the recommended maximum (20mL/kg) in all the trials; patients with coagulopathy or renal dysfunction had been excluded by the trial protocols of most studies. Therefore the patients were a lower-risk population than might be typical of routine clinical practice.

With respect to blood loss over the first 24 hours, there was a statistically significant reduction with the use of albumin versus HES, and this was apparent in trials of both pump priming and in trials of volume expansion. The bleeding difference was similar in magnitude whether the comparison was from albumin to medium molecular weight HES or to high molecular weight HES (Table 4).

HES molecular weight	n trials analysed	SMD* for bleeding
High (450 kDa)	9	- 0.27 (-0.49 to -0.05)
Medium (200 kDa)	8	- 0.21 (-0.44 to 0.01)
Total †	17	- 0.24 (0.40 to - 0.08)

*, SMD, standard mean difference; †, one trial included both high and medium molecular weight HES; negative numbers favour albumin

Table 4 Standard mean difference for bleeding: albumin versus high or medium molecular weight HES:

In adult trials, the pooled mean blood loss in albumin group was 693(350mL compared with 789(487mL in HES group. The estimated proportion of adult albumin recipients with blood loss >1000mL was 19% compared with 33% of adult HES group patients. Triggers for intervention will vary from centre to centre, but 1000mL is one of the published triggers that might trigger delay in extubation, administration of blood products or re-exploration for bleeding. The re-operation rate was lower in the albumin group, but only 10 of the 16 trials reported data on this so it cannot be concluded that the difference is statistically significant, but the differences were similar in magnitude for medium or high molecular weight HES. Therefore:

- Albumin does not worsen outcome
- Does not decrease survival in the acutely ill and, based on evidence of higher-quality trials may confer survival benefit
- Based on extensive evidence, albumin reduces morbidity in the acutely ill
- When used for pump priming or volume expansion, albumin decreases post-operative bleeding in CPB patients compared with HES
- Albumin is associated with less bleeding after CPB compared with both high and medium molecular weight HES

Hypoalbuminaemia in the acutely ill - risk and rationale for treatment: a meta-analysis:

Poster presentation

Roberta Navickis,
Jean-Louis Vincent, Marc-Jacques Dubois and Mahlon Wilkes

Although hypoalbuminaemia is associated with poor outcome, the causal role of low serum albumin and the appropriateness of albumin therapy are controversial. The authors conducted a meta-analysis of cohort studies with multivariate analysis capable of more accurately assessing whether serum albumin is a direct contributor to poor outcome, rather than just a marker for other pathological processes. They also examined controlled trials of albumin therapy for hypoalbuminaemia that reported data on morbidity, which - as Dr Wilkes had mentioned in his presentations - may afford a comparatively sensitive endpoint.

The pooled results of the meta-analysis of 66 cohort studies, with a total 171,654 patients, revealed hypoalbuminaemia to be a potent and concentration-dependent, independent predictive factor for poor outcome. For each 10g/dL decline in serum albumin concentration, the odds of mortality increased by 124% (OR, 2.24, CI, 1.83-2.74) and morbidity, intensive care stay, hospital stay, and resource utilisation were also increased.

The effects of hypoalbuminaemia were independent of nutritional status and inflammation.

In analysis of seven prospective controlled trials of albumin therapy to correct hypoalbuminaemia, that included a total of 449 patients, albumin therapy reduced complications of hypoalbuminaemia, although the overall effect was not statistically significant. However, there was a strong and statistically significant (P=0.019) inverse relationship between morbidity and the attained serum albumin level. Morbidity was reduced when the attained serum albumin was above 30g/L.

The authors draw the conclusion that the value of albumin treatment for hypoalbuminaemia needs to be investigated further and in well-designed randomised controlled trials. However, they consider that the evidence suggesting a causal link between hypoalbuminaemia and poor outcome, and a dose-dependent effect of exogenous albumin in reducing complications provides a logical basis for albumin therapy.

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22nd International Symposium on Intensive Care and Emergency Medicine*

*This publication is produced with the aid of an unrestricted educational grant from
The Plasma Protein Therapeutics Association Europe
Boulevard Brand Whitlock 114/5
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