

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

Human serum albumin - more than fluid replacement

Report of a session of the Austrian International Congress 2001,
held at the Hofburg Congress Centre, Vienna, Austria:
12-14 September, 2001

The Austrian Society of Anaesthesiology, Resuscitation and Intensive Care Medicine (ÖGARI) was founded in October 1951, with the First Austrian Congress for Anaesthesiology held in the inaugural year. The role of the anaesthetist in intensive care medicine has developed extensively in recent years and the Austrian International Congress in 2001 was held in collaboration with the Austrian Society of Anaesthesiological and General Intensive Care Medicine (ÖGAAIM) and the Austrian Association of Nursing in Anaesthesia and Intensive Care (ÖBAI).

A session, sponsored by PPTA Europe, was held as part of the ÖGARI general assembly on the topic of "Human serum albumin - more than fluid replacement". The Chairman, Professor Alfons Hammerle (University Hospital, Vienna) welcomed the audience on behalf of the PPTA and of the ÖGARI.

In his introduction, Professor Hammerle said that the role of albumin has been the subject of critical debate over the past few years. Not only the economic aspects of using albumin compared with other colloids, but also questions concerning outcome in critically ill patients have given new impetus to the discussion.

The Cochrane Injuries Group article in the British Medical Journal in

1998 (**317**, 235), on the basis of meta-analysis of several studies of critically ill patients, concluded that the mortality of patients receiving albumin increased under certain conditions. The initial discussion of this report was heated and its findings considered controversial, but nevertheless, many have accepted its validity. This acceptance has gone so far that many clinicians think that albumin has no place in modern fluid or nutrition management. The widespread belief, which Professor Hammerle described as "almost mythical", that albumin was not only expendable, but even dangerous, led to a worldwide decrease in its use.

On one hand clinicians are faced with the Cochrane report of an increase in mortality in certain subgroups of albumin-treated patients compared with recipients of crystalloids, and on the other there is data from the National Veterans' Administration Surgical Risk study (Gibbs *et al*, *Arch Surg*, 1999, **134**, 36) where investigations were carried out on patients who underwent major, non-cardiac surgery. Pre-operative albumin measurements on over 54,000 patients, gathered for the purpose of risk analysis, showed dramatic results. Mortality rose exponentially from a low of less than 1% in association with serum albumin levels greater than 46g/L to a high of 29% when albumin levels were less than 21g/L. No

other individual risk factor was as significant as the serum albumin level.

These two viewpoints present a clinical and academic challenge and, in introducing and welcoming Dr Steffen Mitzner from Rostock, Germany, and Professor Dr Jean-Louis Vincent from Brussels, Belgium, Professor Hammerle hoped that the speakers would be able to help the audience to make a more informed opinion.

Use of albumin in a liver support device (MARS); basics and clinical results

Dr Steffen Mitzner, Rostock, Germany

The Molecular Adsorbent Recirculating System (MARS) has been

developed as a system to help the treatment of liver failure patients using an extracorporeal detoxification mode.

Background to the MARS

In liver failure, as in kidney failure, there are increased plasma levels of end products of metabolism that may become toxic if they are not sufficiently cleared. These include:

- Bile acids
- Bilirubin



Dr Steffen Mitzner

- Prostacyclins
- Indol/phenol metabolites
- Toxic fatty acids
- Dioxin and diazepam-like substances
- Ammonia
- Lactate

Accumulation of these compounds leads to depression of brain, kidney and cardiovascular function and of bone marrow activity; further it induces liver damage (hepatocyte necrosis and apoptosis) and thus maintains a vicious circle of organ damage. The difference in the liver, in comparison to the kidney, is that a number of these compounds are not water soluble, but require protein transport. In addition, their accumulation can be linked to certain features of liver failure that can be seen as secondary to the initial liver dysfunction.

As albumin serves as the single most important transport protein for all these metabolites, the idea developed to devise a system for liver failure patients that would be safe and efficient in removing albumin-bound toxins, the MARS (Figure 1). This consists of an extra-corporeal standard blood circuit with a central venous catheter.

The concept of albumin dialysis

Whole blood is run through the lumen of a hollow-fibre module, the MARS module. The membrane of the module has relatively open pores on the outer, compared with the inner, surface and allows adsorption and desorption of albumin-bound substances (Figure 2). These are adsorbed from the plasma albumin of the patient, onto the membrane surface with

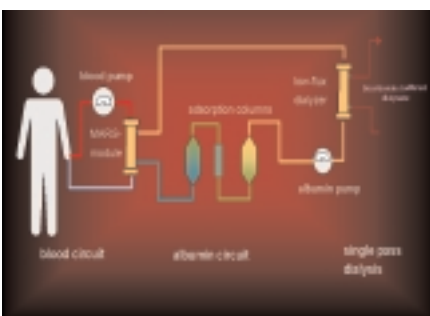


Figure 1 The Molecular Adsorbent Recirculating System (MARS)

desorption to the external, dialysate side, allowing passage of the toxic substances from the blood to the dialysate compartment, following a concentration gradient. If there is high bilirubin in the blood, but not externally, this is the driving force for bilirubin through the membrane. The albumin molecules in the patients are overloaded, because the liver cannot - for different reasons - deal with these metabolites. The main difference, compared to kidney dialysis, is the presence of pure human albumin as the acceptor molecule in the dialysate. As the membrane is more open towards the dialysate side, the dialysate albumin takes up the metabolites.

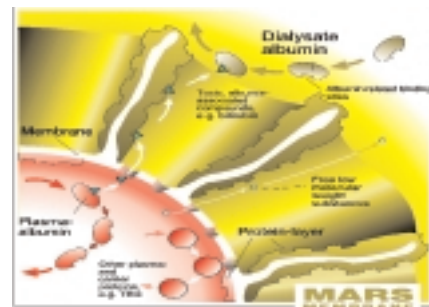


Figure 2 The MARS membrane

The exchange is effective because the distance between the blood and the dialysate is short, in the order of less than 1 micron. As shown in Figure 1, the albumin-rich dialysate is re-circulated through a closed loop circuit, involving a charcoal and an anion exchanger resin adsorption column, then a second, standard dialyser to remove water-soluble toxins, filtrate and buffer the patient, to balance sugar and electrolytes as needed.

Initial evaluation of the MARS

As this is a pure detoxification device, it was easy to evaluate to the first step - are particular metabolites removed in a clinical setting? This has been demonstrated with:

- Bile acids - which are important in decompensated liver failure.
- Bilirubin - which may induce

necrosis and apoptosis of hepatocytes as well as kidney tubular cells and probably other cell types. (This is also true for bile acids).

In a single 6-hour treatment with the MARS, in a clinical setting, both bile acids and bilirubin were significantly decreased in patients with chronic liver failure and acute decompensation, with significantly superior results to those achieved with haemodiafiltration.

- Tryptophan, a precursor of serotonin, which may have a role in hepatic encephalopathy, was more effectively removed by MARS than by standard haemodiafiltration.
- Medium and short chain fatty acids.
- Ammonia is fairly well removed by conventional dialysis, but MARS improves the removal of ammonia and creatinine.

The clinical benefits of MARS

There are data to show that a number of albumin-bound and water-soluble metabolites can be removed in liver failure patients, but what are the clinical benefits?

Cerebral function

In an elegant pilot trial conducted in Copenhagen (*Schmidt et al, Liver Trans, 2001, 7, 709*), flow velocity was determined by transcranial ultrasound. It was found that, in seven of eight cases where measurements were available from before and after a single 10-hour MARS treatment, there was a clear picture of an increase in cerebral blood flow in patients with acute decompensation of chronic liver disease. In another study (*Crit Care Med, 2001, 29, 1332*) Sorkine *et al* followed three closely monitored patients. During MARS treatment there was a fall in intracranial pressure (Figure 3). There were no controls in this study, but other reports of small cohorts and isolated patients confirm this finding of lowered intracranial

pressure. This may be clinically relevant in liver failure, but more and confirmed data are required. This evidence strongly suggests that there is a chance to influence, clinically, hepatic encephalopathy. This has been evaluated in a

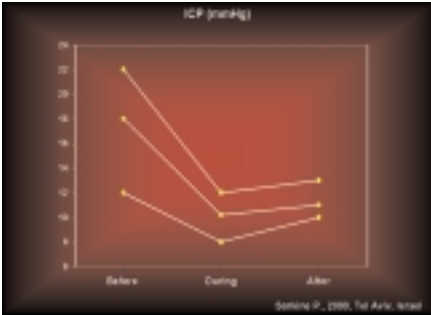


Figure 3 Intracranial pressure before during and after MARS treatment in three patients with acute exacerbations of chronic liver disease

number of trials by different groups, including one at Dr Mitzner's own centre (Stange *et al*, *Liver Trans*, 2000, **6**, 603), where patients with acute decompensation of chronic disease were studied.

Using the 4-grade encephalopathy scale, at the time of hospital admission this group of 26 patients had some minor encephalopathy.

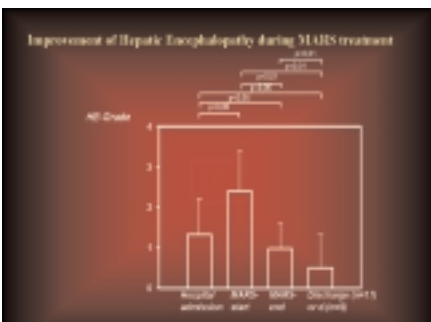


Figure 4 Improvement in hepatic encephalopathy during MARS treatment

Encephalopathy became worse during the phase of standard clinical treatment. Through a course of five to six single MARS treatments, there was a significant fall in encephalopathy. Encephalopathy remained stable, without further MARS treatment, to death ($n=9$) or hospital discharge ($n=17$).

The Copenhagen group (Schmidt *et al*) also reported an increase in systemic vascular resistance during a single 10-hour treatment, a finding that has been reported in other small cohort studies. This might explain the reports from other groups that there is an increase in mean arterial pressure that is unusual in critically ill patients undergoing extracorporeal circulation.

Kidney function

There is a fall in plasma renin activity during MARS treatment, not due to removal of plasma renin, but rather as a reaction to changed haemodynamics. This may explain the improvement in renal output reported patients with in hepatorenal syndrome (HRS). Three patients with HRS went from a virtually oliguric state to a renal output around 1.5L/day with a series of individual MARS treatments (Mitzner *et al*, *Liver Trans*, 2000, **6**, 277).

Liver function

Toxicity testing of patients' plasma sampled before and after MARS treatment, using primary rat hepatocytes, showed cell-damaging effects of jaundiced plasma that were not observed after MARS treatment.

Clinically there are a number of reports, of different quality, indicating that these different indicators for liver protein synthesis increase during a course of MARS treatments (Box 1).

Following the Child-Turquotte-Pugh (CTP) or Child scores through treatment, patients that were initially quite ill with a Child score of C (CTP 12-13) were improved to Child B (CTP 9-10). This improvement was stabilised or maintained without further MARS treatment (Stange *et al*, *Liver Trans*, 2000, **6**, 603).

- Prothorombim activity (Quick) (%) ↑
- Antithrombin III ↑
- Factor VII ↑
- Albumin ↑
- Cholinesterase ↑
- Partial thromboplastin ↓
- International Normalised Ratio ↓

Box 1 Indicators of improved liver function in patients undergoing MARS treatment

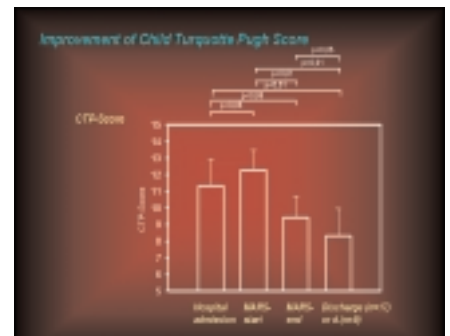


Figure 5 Improvement in Child-Turquotte-Pugh Score with MARS

Skin

Only a relatively small number of patients have been treated, but there is some evidence that two to three MARS treatments per patient could be useful to treat patients with intractable pruritus in different syndromes such as cholestatic syndrome.

Clinical trials with the MARS

A number of trials have been done to date and there have been uncontrolled pilot trials that followed protocols. Pilot studies and individual case reports have concerned patients with:

- alcoholic liver disease
- chronic disease
- fulminant hepatitis
- acute hepatic failure
- primary non-function

In addition there are completed or ongoing prospective controlled trials.

Hepatorenal syndrome

In the small study published in 2000 (*Liver Trans*, **6**, 277),

Dr Mitzner's group were able to demonstrate a significant survival difference for patients with Child C with cholestasis (bilirubin >20mg/dL) and HRS Type 1-2. This study was performed at two centres, with 13 patients, and compared results with MARS and conventional haemodiafiltration (HDF). Compared with HDF, MARS treatment resulted in:

- Prolongation of survival time (Figure 6)
- *In vivo* reduction of protein bound and unbound toxic molecules
- Improvement of coagulation parameters
- Increase in plasma sodium
- Increase in blood pressure
- Improvement in renal function

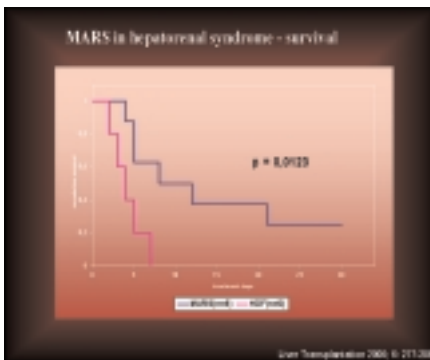


Figure 6 MARS in hepatorenal syndrome - survival compared with conventional haemodiafiltration (HDF).

A further controlled trial conducted in collaboration with the University of Essen has just been completed. The patients enrolled had chronic liver failure with acute decompensation and intra-hepatic cholestasis and bilirubin levels >20mg/dL unresponsive to standard treatment within a pre-trial phase of three to five days. Of the patients 46 patients initially recruited, 22 were excluded on the grounds of liver function or because they improved during the pre-phase leaving 24 patients to be randomised into two groups of 12, either to continue with standard medical treatment or to having additional MARS treatment over 11 days (Figure 7).



Figure 7 Protocol for Essen/Rostock collaborative study of MARS in patients with liver failure and intra-hepatic cholestasis

Patients were Child B or C, with high bilirubin levels (30mg/dL), some encephalopathy, some impairment of liver synthesis function and some kidney dysfunction. In a 30-day observation period, one of 12 MARS-treated patients died compared with six of the control-treated patients who received best practice care.

At randomisation, patients had hepatic encephalopathy around Grade 1. Over the MARS treatment period, there was a significant decrease in encephalopathy in the MARS treatment group, but control patients showed increases. MARS-treated patients remained stable with respect to encephalopathy until the end of the observation period. The mean arterial pressure fell in controls, but slightly increased in the MARS group, and remained stable without further MARS treatment after 11 days. Creatinine was slightly increased at baseline; MARS removed creatinine, while levels increased in control patients, resulting in a significant difference between levels in the two groups after one week, which was maintained.

Many hepatologists now use the Mayo Endstage Liver Disease Score (MELD) that predicts mortality better than does the Child score. The predicted 30-day mortality, at baseline was 50% for controls and 45% for the MARS-treated

patients. The observed 30-day mortality was 50% in standard medical treatment (control) group, but only 8.3% in the MARS-treated patients (Figure 8).

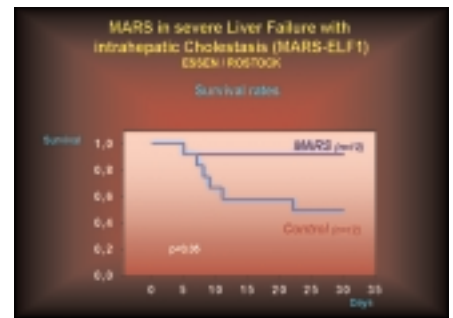


Figure 8 Survival rates in patients in severe liver failure with intra-hepatic cholestasis receiving standard medical treatment (control) or standard medical treatment plus MARS

Future studies

Hepatic encephalopathy is the indication in the FDA approval trial for MARS and recruitment is ongoing at five centres in the USA. A study in patients with chronic liver disease has just started in seven centres in Europe.

A study in Germany has included patients who underwent surgery and developed a liver dysfunction with an increase in bilirubin at least 8mg/dL. These patients had no previous history of chronic liver insufficiency and/or sepsis. MARS treatment was stopped if there was a stable bilirubin <6mg/dL. Results are favouring MARS treatment and an interim analysis shows improved survival among MARS-treated patients.

Conclusions

- Clinical use of MARS treatment was started in 1993 and now more than 60 centres, mainly in Europe, but also in the USA and Asia, have treated more than 800 patients in different indications.
- The indications have included acute on chronic hepatic failure, acute hepatic failure, primary non-function and others.
- The MARS system successfully removes albumin bound as well as water-soluble substances.

- Treatment has been tolerated well - no severe adverse events have been observed.
- Clinical effects have been noted in improvement of cerebral, haemodynamic, kidney and liver function.
- Increased survival in the MARS group, compared with controls, could be demonstrated in two randomised controlled trials.
- More controlled randomised trials are currently in progress to give more information about the capabilities of the system.

Is there still a place for albumin?

Professor Jean-Louis Vincent
Brussels, Belgium

In this era of evidence-based medicine the question arises, what evidence is there for administering albumin to the acutely ill patient?



Professor Jean-Louis Vincent

However, one must not be too insistent about requiring evidence of benefit of certain interventions; there are a number of therapeutic interventions used regularly in anaesthesia and intensive care medicine that are not based on good evidence, for example,

- blood transfusion,
- pressure controlled ventilation, and
- pacemakers for bradyarrhythmias
- use of one versus another adrenergic agent in shock states.

Whilst there are few good data on albumin in acutely ill patients, there are few adequate studies of many other therapeutic interventions in the intensive care unit (ICU.) Should albumin be used in acutely ill patients? There is no

proof that it helps, but there are a number of pathophysiological elements that support the use of intravenous albumin.

Pathophysiological evidence of the value of albumin

Hydrostatic and oncotic pressures
The pathophysiological evidence of the value of albumin begins with the Starling equation (Box 2); the amount of fluid being filtered in the microvasculature depends on permeability coefficients and driving pressure, that is, the hydrostatic and oncotic pressures. Taking pulmonary circulation as an

for any reason the hydrostatic pressure is increased then the oncotic pressure becomes protective. If colloids are given too rapidly, the hydrostatic pressures may be increased too much. When albumin or other colloids are given, caution should be exercised, in order not to increase hydrostatic pressures too significantly.

Leaky capillaries

Many acutely ill patients have an altered reflection coefficient (Starling Law, Box 2). The capillary membrane characteristics are altered because the patient is septic and in an inflammatory

Filtration = Permeability x Driving pressure

$$Q = K_F \{ (P_{mv} - P_{pmv}) - \sigma (\pi_{mv} - \pi_{pmv}) \}$$

Where P_{mv} and P_{pmv} are the capillary (microvascular) and interstitial (perimicrovascular) hydrostatic pressures, respectively, and π_{mv} and π_{pmv} capillary and plasma protein osmotic pressures, respectively. K_F is the filtration coefficient and σ is the reflection coefficient.

Box 2 The Starling Law

example, in normal conditions the extravascular lung water starts to increase when the hydrostatic pressures increase above a critical value. In classical experiments in dogs reported by Guyton and Lindsey (*Circ Res*, 1959, 649), the critical value was 24mm Hg. This would be a wedge pressure of 24mm Hg in a patient. However, in the presence of hypo-oncotic, induced in these experiments by plasmapheresis, this critical pressure was much lower. If the patient is in a hypo-oncotic state, he will develop pulmonary oedema at a much lower hydrostatic pressure than in baseline, or normal, conditions. Therefore, in the hypo-oncotic patient, increases in hydrostatic pressures must be avoided.

When the capillary permeability is normal, if the hydrostatic pressure and wedge pressure are also normal, the oncotic pressure is not particularly significant. However, if

state. Therefore, the situation may be altered in the patient with leaky capillaries. The colloid osmotic pressure within the vessels may be somewhat reduced, because there is albumin in the interstitium due to leakage of larger molecules out of the intravascular space. So, even when the hydrostatic pressures are normal, there may be a continuous egress of fluid, which again must be picked up by the lymphatic system. Even when the pressures are not increased there may be a greater passage of water into the interstitium.

It is suggested, in the literature, that leaky capillaries worsen oedema, because there will be a higher oncotic pressure in the oedema fluid, although Professor Vincent maintains that the oncotic pressure should also increase in the blood. Jing et al (*J Surg Res*, 1982, **33**, 482) performed one of the very few studies addressing this issue. In a study of permeability

pulmonary oedema, they randomised dogs receiving oleic acid, as a model of acute respiratory distress syndrome (ARDS), to receive albumin or Ringer's lactate (RL). They hypothesised that albumin would make the oedema worse. In the event, the results, based on the wet to dry ratio in any organ examined, showed that the oedema was actually greater in the RL group than in the albumin group. In the lung there was no significant difference between the two treatment groups; extravascular lung water was, if anything, greater in the RL group, despite the fact the wedge pressure was pushed to higher levels in the albumin group. Thus, there was no evidence that albumin made the oedema worse and the authors concluded that "neither albumin nor large volumes of crystalloid worsened pulmonary oedema, as long as the hydrostatic pressure was kept at normal levels."

Fluid volumes and development of oedema

In terms of volumes of fluid administration, it is worth returning to simple elements. It must be remembered that of the 45 litres of total water in the body, about 15L consists of extracellular fluid; this includes 10L of extravascular fluid and 5L of blood. Therefore, there is twice as much extravascular fluid as blood. If a colloid solution is given, the space of distribution will be about one third the space distribution of crystalloid solutions. There is no doubt of the fact that to achieve the same endpoints when crystalloids are given, three times more volume is needed than when colloids are given. The consequences may be a matter of discussion, but not this basic fact.

If the blood volume is restored with crystalloids, it may not be maintained for the same period of time as when colloids are used

(Wang *et al*, *J Surg Res*, 1991, **50** 163) and fluid administration may be need to be repeated. There is no controversy about this as such; the discussion concerns whether this is good or bad. Those who advocate crystalloid use would say that the resultant oedema is of little consequence. However:

- Oedema in the lungs may impair gas exchange
- Oedema in the periphery it may impair oxygen availability to the cells
- Oedema in the surgical patient may alter wound healing
- Oedema may result in gut dysfunction and impair feeding
- Oedema may result in myocardial dysfunction
- Oedema may facilitate development of cutaneous lesions and decubitus ulcers, especially if the patient is becoming adynamic because of all the water in the interstitium.

There is no good evidence in the literature that any of these matters significantly, but these are important points for any practitioner.

Clinical evidence of the consequences of oedema

However, clinical evidence is beginning to appear in the literature and a recent paper by Lang *et al* (*Anesth Analg*, 2001, **93**, 405) concerned colloids versus crystalloids and tissue PO₂ in patients undergoing major abdominal surgery. Although this was a study with HES, the findings probably do not reflect a specific property of HES versus another colloid such as albumin. Looking at the microcirculation in the periphery, the authors showed that the tissue PO₂ increased significantly with the colloid and decreased with the crystalloids. This is probably primarily related to the fact that these patients, in the first 24 hours following major abdominal surgery including their

time in the operating room, were given 6L of fluid in the colloid group, but almost twice as much (11.74L) in the crystalloid group. This is not surprising, as it is agreed that more volume is necessary with colloids. This may result in more oedema, and this study provides evidence that this may result in impairment in oxygenation.

Hypoalbuminaemia

Would there be any advantage in being hypoalbuminaemic during acute illness? It is hard to imagine why. If hypoalbuminaemia develops, it can be because there is reduced production of albumin due to:

- inflammation,
- malnutrition,
- liver dysfunction and
- re-prioritisation with the increased production of acute phase reactants.

There may also gastrointestinal, renal and cutaneous losses. Vasodilation may result in dilution of the albumin pool, as patients with an inflammatory response are vasodilated and have a higher plasma volume. They may also lose albumin into the interstitium as the capillaries are leaking.

A number of studies have shown that hypoalbuminaemia is associated with increased mortality rates and other adverse events (Box 3), but it could be argued that this is just an association and there is no cause and effect relationship.

Prolonged length of ICU stay and hospital stay
Increased rate of re-admissions
Energy - pro-inflammatory response
Low T3 response
Immobilisation
Diarrhoea
.... A number of secondary effects.

Box 3 Adverse events associated with hypoalbuminaemia

Mangialardi *et al* (*Crit Care Med*, 2000, **28**, 3137) recently looked at hypoproteinaemia in patients with sepsis and showed that patients having low protein concentrations usually have somewhat lower blood pressure and develop ARDS more commonly. Mortality from ARDS was significantly greater in patients with low protein concentrations than in patients with normal protein concentrations (Figure 9). Therefore, there is some trial evidence to indicate that low albumin concentrations are associated with increased complications

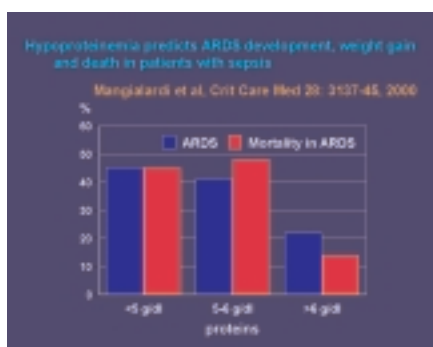


Figure 9 Association of hypoproteinaemia with ARDS development and death in patients with sepsis

Clinical studies of fluid administration

It is a general agreement that more good-quality studies of fluid administration are required, but clinical studies looking at sound end points in this field are difficult to conduct. The studies the 1970s and early 1980s, basically showed no significant difference between colloids and crystalloids. One could do a meta-analysis, such as that published by the Cochrane group in 1998 (Schierhout and Roberts, *Brit Med J*, 1998, **316**, 961) and find, not surprisingly, that there is no significant difference when these studies are put together. However, studies analysed are of limited size and not of good quality.

The medical profession seems to have been more impressed by the meta-analysis from the Cochrane group (*Brit Med J*, 1998, **317**, 235)

of 30 randomised trials involving 1419 patients. Pooling results, the relative risk of death in albumin recipients is calculated as 1.68 and the 95% confidence interval is 1.26-2.23 and, therefore, statistically significant. This referred to burn patients and those with hypoalbuminaemia. The sentence in the report that has been most remembered is that "these data suggest that for every 17 critically ill patients treated with albumin there is one additional death". This is a very provocative statement. What might be the explanation? Is it due to:

- Fluid overload / pulmonary oedema, because the filling pressure is increased too much? This is unlikely.
- Altered myocardial contractility due to decreased calcium availability? This is unlikely.
- Worsening of oedema? This is not likely, because the increase in albumin should result in increased plasma concentrations as well as peripheral concentrations.
- Increased blood losses? This is unlikely.
- Impaired water and sodium excretion due to renal failure? This is unlikely unless very high colloid osmotic pressure is reached.
- Altered immune response? This is not known.

There is nothing to explain the results of this meta-analysis, if the results are indeed valid. A more recent, and probably better performed meta-analysis, included 55 trials (Wilkes and Navickis, *Ann Intern Med*, 2001, **135**, 149). With reference to patient survival, the authors conclude that: "Overall, no effect of albumin was detected; any such effect may therefore be small. This finding supports the safety of albumin. The influence of methodologic quality on relative risk of death suggest the need for further, well-designed clinical trials."

Meta-analyses have their drawbacks (Box 4) and are primarily devised to generate hypotheses, but there are also specific problems in trials including albumin and these involve patient crossovers. If study patients are randomised patients to albumin or crystalloids, and a patient is in the albumin group but doing poorly, he will probably be kept in that group. If the patient is randomised to crystalloid administration and is doing poorly, crossover to the albumin group may well be considered. There are some crossovers in these reported studies, and they all go in the same direction. Patients doing poorly, going into multi-organ failure are sometimes crossed to the albumin group.

Heterogeneity of studies
Heterogeneity of patient populations
Small populations studied

Box 4 Drawbacks of meta-analyses

Benefits of albumin for specific patients

There is evidence of specific benefit of albumin for subgroups of patients, particularly in the gastroenterology literature. Gentilini *et al* (*J Hepatol*, 1999, **30**, 639) studied patients with cirrhosis and severe ascites, randomised to receive diuretics alone or in combination with albumin. The duration of hospital stay was significantly reduced when they gave albumin and also there were fewer re-admissions at 12 months (Box 5). There was a sustained advantage in giving albumin to these patients.

Gines *et al* (*Gastroenterol*, 1988, **94**, 1493) had made similar observations in patients with cirrhosis in a randomised comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. In 105 patients, there were lower renin and aldosterone concentrations a lower incidence

Box 5 Parameters of response to diuretics in patients with cirrhosis and ascites receiving no additional treatment or additional albumin.

126 patients with severe ascites			
	Diuretics alone	Diuretics plus +12.5g albumin / day	P
Phase A			
Hospital stay (days)	24 ± 2	20 ± 1	<0.05
Phase B			
Ascites at 12 months	30 %	19 %	<0.05
Re-admission at 12 months	27 %	15 %	<0.05

of hyponatraemia and lower incidence of renal failure in recipients of albumin. More impressive are the results from Sort et al (*N Engl J Med*, 1999, **334**, 403) on the effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. Patients were treated with antibiotics, with or without additional albumin (1.5g/kg on day 1, and 1g/kg on day 3). Hospital mortality was 10% in albumin recipients compared with 29% without albumin.

One might consider that there are many other factors at work in the cirrhotic patient, but with regard to the release of various mediators and vasodilation, there are many common features with sepsis. Hypoalbuminaemia, cytokines, nitric oxide and vasodilation all lead to a hyperdynamic state.

In the field of renal transplantation, the transplant surgeons often report that when the donor has received colloids, the organs are less oedematous; the surgeons prefer it. The data may not be robust, but it is a clinical observation.

Current studies

Very recently, Martin *et al* have completed a limited study in patients with ARDS, to determine whether albumin administration would improve the lung function. (*Crit Care*, 2000, **4** (Suppl. 2), S21). It was found that in contrast to some previous opinions, administration of albumin

significantly increased serum albumin levels in these acutely ill patients. Body weight went down in albumin recipients more than in placebo recipients and oedema was reduced. There was also transient improvement in gas exchange, with a change in the PaO₂:FiO₂ ratio but this disappeared at three days. There was some evidence of shorter duration of mechanical ventilation, or rather a greater number of ventilator-free days, in patients receiving albumin. This is a pilot study, and certainly not definitive, but interesting nonetheless.

Professor Vincent's own group in Brussels is conducting a randomised study in 100 patients looking at the effect of correction of hypoalbuminaemia in acutely ill patients. This study is almost complete and results will be available within months. There are larger studies in progress in Australia and in France, looking at the effect of albumin administration on survival of acutely ill patients.

Additional properties of albumin

Professor Vincent mentioned some other properties of albumin that must be kept in mind.

- Albumin carries a number of substances in the blood, - enzymes, bilirubin, hormones, trace metals, fatty acids, reactive oxygen species.
- Albumin is an antioxidant.
- Albumin is involved in drug transport, in particular antibiotics, phenytoin, lidocaine,

which may be important in terms of drug metabolism. Hypoalbuminaemia may result in increased concentrations of free drugs, which may, theoretically, lead to higher, potentially toxic doses of antibiotics in hypoalbuminaemic patients.

- Hypoalbuminaemia may promote platelet aggregation. Albumin is a natural anticoagulant, limiting platelet aggregation. This may or may not be of significance, but there is enormous interest currently in the interaction between coagulation and inflammation.

Neuroprotective effects

The neuroprotective effects of albumin (Belayev *et al*, *Stroke*, 2001, **32**, 553) have been investigated in rat model of middle cerebral artery occlusion. The work is important because these authors could show that albumin administration could reduce brain swelling, improve neurological function after 24, 48 and 72 hours and reduce infarction volume following the middle cerebral artery occlusion. The interventions were made up to four hours after the onset of ischaemia. These authors have done a number of studies, and these results are important because it is within four hours that intervention is a practical, clinical proposition. It may be difficult to extend this work to patients, because studies in stroke patients need such large numbers of patients to demonstrate benefit.

Albumin versus artificial colloids

A number of things touched on by Professor Vincent can apply to albumin and to artificial colloids, and it may be said that artificial colloids are cheaper. However, the limitations of these solutions are also known. They are cheaper, but gelatins are not very effective. Dextrans may be more efficient, but there are well-known problems

with allergic reactions. HES are very useful but also have limitations of accumulation in the reticuloendothelial system, alteration of haemostasis, allergic reactions and some associations with renal dysfunction.

A meta-analysis by Wilkes, Navickis and Sibbald of albumin versus HES in cardiopulmonary bypass surgery (*Ann Thoracic Surg*, 2001, **72**, 527) concluded that postoperative bleeding was significantly lower in cardiopulmonary bypass patients exposed to albumin than HES. Studying the effects of HES and gelatin on renal function in severe sepsis, (Schortgen *et al*, *Lancet*, 2001, **357**, 911), concluded that HES may alter renal function in severe sepsis. This was observed with one particular HES solution and it may not occur with others, but it confirms the message that no matter which artificial colloid is chosen, there are limitations.

Even though albumin is more expensive, it has a number of qualities, including its transporting properties, antioxidant properties, good tolerance and the facility of easy monitoring. Therefore, albumin preparations may be expensive, but may also be cost effective, when the advantages are taken into account. Professor Vincent has recently published an article, " Fluid Management - The Pharmacoeconomic Dimension (*Crit Care*, 2000, **4**, S33) summarising this aspect.

It must be concluded that there is insufficient good clinical data on albumin administration in humans, but there are a number of pathophysiological elements and preclinical work that need to be taken into account. Of course, it is generally agreed that there is a need for prospective clinical studies, and these are now ongoing around the world. In the meantime, in Professor Vincent's opinion, and especially in view of the meta-analysis by Wilkes and

Navickis, there is no reason to ban albumin administration. Further studies are needed, but there is still a sound rationale for the use of albumin in acutely ill patients.

Discussion

After the presentations Professor Hammerle suggested that the question for clinicians is how to find the ideal plasma volume expander. The fluid should provide immediate plasma volume expansion capability at low volume, be able to exert an oncotic pressure equal to that of plasma, with minimal effect on coagulation, be free of viral and bacterial contamination and have a prolonged half life in the circulation without accumulation. There should be no pharmacological interactions and it should be cost-effective. Is there a way of finding this ideal volume expander?

Professor Vincent said that not only was this impossible, it was not necessary. There is a need for a number of solutions to be available, just as there are a range of drugs available for other indications; one uses the one that the patient requires at the time, and often in combination. The same applies for intravenous fluids. A patient who is profoundly dehydrated because they have not been able to drink for several days does not need colloids, just crystalloids to replace water and perhaps some salts. On the other hand, considering a patient with anaphylactic shock, it is known there is significant loss of albumin in these conditions, and colloid treatment would be favoured. Sometimes red blood cells are needed. So there is a need to have the different solutions available.

Professor Hammerle agreed. Doctors are increasingly called upon, by the financial managers of their hospitals, to justify the use of expensive treatments; some departments find, for example,

albumin to be essential, while others shun it. We need to discuss not only the price, per se, but also cost effectiveness. However, as Professor Vincent said, arguments will go on forever, but without data it is impossible to make strong recommendations.

In drawing the meeting to a close and thanking the speakers for their contributions, Professor Hammerle said the well-established and important functions of albumin in health had been demonstrated, but it is important to distinguish between health and critical illness. There is a need for evidence of correlations between blood albumin levels and colloid osmotic pressure. It appears that drug binding by albumin plays an important role, but there is no clear evidence that the increased free fraction of drugs in patients with hypoalbuminaemia is of clinical significance. Many questions are still open concerning the choice of fluid resuscitation and Professor Hammerle said that he found it a puzzle why the theoretical advantages of albumin have not yet been fully verified in clinical practice. It is obvious that there is a definite need for accurate investigations to identify those patients who would benefit.

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