PPTA EUROPE
Plasma Protein Therapeutics Association

Progress in Albumin Research

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

Albumin - IV fluids

Summary of sessions of the 21st International Symposium on Intensive Care and Emergency Medicine (ISICEM) held at the Brussels Congress Centre, March 20-23, 2001

Introduction

The International Symposium on Intensive Care and Emergency Medicine continues to be the major congress in this therapeutic area, attracting larger numbers each year and providing a forum for discussion, education and presentation of research results. The Chairman, Professor Jean-Louis Vincent, welcomed nearly 4000 delegates to 21st International Symposium at the Brussels Congress Centre.

While advances continue to be made in the management of sepsis, techniques of ventilation and monitoring, fluid management remains a fundamental feature of caring for the critically ill patient.

Intravenous fluids - A continuing debate

The controversy concerning the optimal choice of fluids for patients in shock will continue until extensive, randomised controlled clinical trials are completed. In the meantime, debates around the topic of "Colloids are superior to crystalloids" will be held regularly at congresses and symposia. At the 21st ISICEM, the session moderated by Neil McIntyre (USA) brought together Professors Jean-FranÁois Baron (France) and Paul Pepe (USA).

Professor Jean-Francois Baron

Professor Baron started by reviewing the meta-analyses comparing crystalloids and colloids, particularly human serum albumin, that have been published in recent years. Schierhout and Roberts (*Brit Med J*, 1998, **316**, 961) compared colloids and crystalloids in critically ill patients and concluded that colloid use was associated with increased mortality. The Cochrane Data Base Systematic Review (2000) meta-analysis showed an increase in mortality in the group of patients treated with albumin. Choi et al, (*Critical Care Medicine*, 1999, **27**, 200) analysed virtually the same data as Schierhout and Roberts, but detected no overall difference in mortality.

These analyses have been controversial and criticised on a number of grounds including the selection of studies for analysis, the small numbers of patients treated in the trials, mixed patient populations, the selection of appropriate outcomes, lack of consistency in the study solutions and the fact many of the studies were performed in the 1970s and 1980s, when the standard of care was hardly that practised today. Also the colloid solutions available were not those in current use. In short, nothing concerning the superiority of one or other type of fluid can be concluded from these meta-analyses. Evidence from studies with sufficient statistical power is required to demonstrate a difference between colloid and crystalloid. Assuming a 15-20% mortality rate in intensive care units, between 5000 and 9000 patients need to be included in a study to demonstrate a significant difference between two interventions.

However, there is indirect evidence in favour of using colloid. Animal data show that colloids are more efficient in restoring mean arterial

pressure and cardiac output, because smaller volumes are required to achieve these endpoints. If duration of resuscitation is an issue, this animal data and clinical findings suggest that colloids are preferable for treating patients in shock.

Animal data also shows that infusion of Ringer's lactate, to three or four times the volume of blood shed, although initially restoring cardiac output may not adequately restore circulation to the small vessels in muscles, in the kidney or the small intestine. Therefore, crystalloids can restore haemodynamics, but there may be problems at the microcirculatory level and better, and quicker, restoration at this level will be obtained with colloids. There is clinical evidence that use of hydroxyethyl starch, rather than gelatin, is associated with less extravasation of fluid and further animal study evidence of benefits of hydroxyethyl starch at the level of the endothelial cells.

As Professor Baron concluded, there are no epidemiological studies on which to base a conclusion as to the superiority of either colloids or crystalloids, the published meta-analyses are not valid. However, there are indirect arguments in favour of colloids, in that smaller volumes are infused, there is likely to be less oedema, colloids are associated with a more rapid restoration of general and microcirculatory haemodynamics, and with better tissue oxygenation. There is also evidence of beneficial effects on inflammation.

Paul Pepe agreed that there is no epidemiological evidence to favour either colloids or crystalloids, and that the shortcomings of the meta-analyses, in particular the variations in patient populations among the studies compared and the absence of comparable endpoints, do not permit valid conclusions. Any comparative studies must take account of different patient populations, the different underlying needs for resuscitation and the choice of appropriate endpoints in their design.

Most would agree that colloids and crystalloids are equally effective during resuscitation, grossly and clinically. Colloids may, indeed, be more suitable for rapid resuscitation, but this may be a problem in a patient with ongoing haemorrhage. Although rapid restoration of blood pressure may be an advantage in a controlled situation, in the trauma patient treated on the street, rapid restoration of blood pressure is likely to be deleterious if there is uncontrolled bleeding or unsuspected internal bleeding, leading to disruption of clots and dilution of clotting factors.

The essence of resuscitation is improving the microcirculation and restoring oxygenation, and Professor Pepe suggested that the answer may lie with the haemoglobin-based oxygen carrying solutions that will become available in the near future.

A new meta-analysis of randomised controlled trials

Both the low rate of reported of fatal adverse events in albumin recipients over more than 50 years of clinical use and the significant mortality reduction demonstrated in albumin-treated patients with spontaneous bacterial peritonitis suggest that albumin administration is not associated with excess mortality. A poster presentation at the 21st ISICEM, by Wilkes and Navickis (*Crit Care*, 2001, **5**(suppl. 1), S54, Abst 116), reported the results of a further meta-analysis to evaluate this hypothesis. Although the Cochrane Injuries Group meta-analysis published in 1998 (*Brit Med J*, 1998, **317**, 325) has been criticised on a number of counts, it has not been shown whether rectifying the suggested flaws - that relevant trials were omitted, heterogeneous trials were combined, the effects of trial design features on outcome were inadequately assessed - would have altered the results.

Wilkes and Navickis's analysis included 55 trials involving 3504 randomised patients, with a total of 525 recorded deaths; 27 trials involved surgery or trauma, 4 burns, 5 hypoalbuminaemia, 6 high-risk neonates, 5 ascites and 8 other indications. The trial inclusion criteria were:

* Candidate trials must have involved a randomised comparison of albumin administration with crystalloid, no exogenous purified albumin,

or a lower dosage of exogenous purified albumin.

* Mortality data must have been available.

Trials were identified by a variety of methods including computer searches of bibliographic databases, Medline and Embase, and the Cochrane Controlled Trials Register and the Cochrane Medical Editors Trial Amnesty of unpublished trials. General medical journals were hand searched and there were inquiries of medical directors and investigators, and examination of reference lists compiled in previous meta-analyses and other articles. Trials were selected, data extracted independently by two investigators and differences resolved by discussion. The primary outcome measure was relative risk of death. Small trial bias was evaluated by the test of Egger et al (*Brit Med J*, 1997, **315**, 629). The design of seven of the 55 trials (13%) included some form of blinding. Mortality was an endpoint of 17 trials (31%). Individual control group patients were crossed over to albumin administration in eight studies (15%).

At least one death occurred in 42 trials (76%). The pooled relative risk of death in these 42 trials was 1.11 (95% CI, 0.95-1.28). Relative risk was not significantly different from unity in any of the six categories of indications or overall. Relative mortality risk was higher by 60% (1.17/0.73) among non-blinded trials and by 49% (1.49/1.00) in trials that did not include mortality as a study endpoint and 38% (1.43/1.04) for trials with cross over. For all trials the adjusted relative risk, taking small trial bias into account was 0.83 (95% CI 0.65-1.08). In trials with blinding, mortality as an endpoint, and no crossover, adjusted relative risk was also less than unity.

The factors that may account for the disparate findings of the current meta-analysis versus that of the Cochrane Injuries Group can be summarised as follows:

* The present meta-analysis included more trials (55 versus 30).
* Four trials with a total of 727 randomised patients, included in the present meta-analysis, were specifically excluded by the Cochrane Injuries Group. Pooled relative analysis for the four trials was 0.94.
* Lack of blinding, absence of a mortality endpoint, crossover and small trial bias are likely to have contributed substantially to the excess mortality observed by the Cochrane Injuries Group.
* The control group mortality in the present meta-analysis was 252/1502 (17%), a substantially higher proportion than the 58 of 608 (10%) in the Cochrane Injuries Group meta-analysis; the patient population in the two meta-analyses differed in their underlying risk.

Thus, there was no evidence of excess mortality in albumin recipients and the analysis suggests that albumin may reduce mortality. The authors conclude that the potential of albumin to reduce mortality should be evaluated in future clinical trials. However, the present findings further support the excellent long-term safety record of albumin.

Factors influencing current intravenous fluid usage

The Symposium session on intravenous fluids was moderated Fabrice Brunet (France) and Michael West (USA).

Professor Fabrice Brunet

Jamie Cooper (Australia) considered the evidence on resuscitation fluids from studies that have influenced recent clinical practice. Since the studies by Schierhout and Roberts and by the Cochrane Injuries Group were published, there has been a 40% reduction in the amount of albumin issued to UK hospitals. Therefore, these studies have influence practice, despite the controversy and correspondence following their publication. Choi et al at McMaster University, using the same data as Schierhout and Roberts, found no clear difference

between crystalloids and colloids, suggested that crystalloids might be associated with lower mortality in trauma, but that methodological limitations preclude evidence-based conclusions. This study had little impact on practice. The subsequent Cochrane Collaboration analysis, available on the Cochrane database (2000) concludes that use of albumin is associated with an increased risk of mortality in some indications with the recommendation that the use of albumin is hard to justify outside the context of randomised trials.

Dr Cooper asked how could such excellent groups arrive at different conclusions using the same data? Part of the answer may come from an editorial in the British Medical Journal, published some time before these studies, entitled 'Misleading meta-analysis' (Egger and Davey Smith, 1996, 310, 752). Mentioning the problems of small-trial bias, they concluded that analyses (such as the colloid versus crystalloid analysis) based entirely on small trials, should be distrusted even if the combined effect in those studies is statistically significant. A further criticism of meta-analyses is that when trials of low methodological quality are included, the treatment effect is usually enhanced.

Examining the studies that appear to have influenced current practice, they can be criticised on the grounds of inappropriateness of the solutions compared, the difference in baseline severity of the patients' conditions, differences in technique in the compared groups, small studies, non-comparable patient populations and the age of the studies. In the McMaster meta-analysis, the investigators were blinded to the nature of the comparisons and worked out a validity score for the methodology of the trial to give a quality valuation for each paper on the basis of randomisation, blinding, population, co-interventions and how was mortality reported. On a scale of 1-16, the majority of papers considered were of relatively low validity and the conclusion of the analysis was that, although there was a trend in favour of crystalloids, it was not statistically significant. Crystalloids were favoured in a sub-group of trauma patients, but the result was heavily influenced by a single study. The grounds for criticism of the Schierhout and Roberts / Cochrane Injuries Group analysis are summarised in Box 1. The grounds for considering the McMaster analysis to be more valid are summarised in Box 2.

* The studies analysed were too small
* Few studies had mortality as an endpoint
* Poor matching for illness severity, mainly because the studies were small
* The studies were not blinded
* Randomisation was poorly described in many of the papers
* The follow up times were variable
* Primary study selection by those who did the meta-analysis
* Technique - a fixed effects model was used (compared with a variable effects model used by the McMaster Group)

Box 1 Grounds for criticism of the Schierhout and Roberts / Cochrane Injuries Group meta-analyses of crystalloids versus colloids

* Papers were graded independently and in a blinded fashion
* Very inferior papers were not considered
* Because of the known heterogeneity of patients, a random effects model was used
* The weaknesses of the primary studies were highlighted

Box 2 Grounds for considering the McMaster analysis (Choi et al) to be superior and with a more valid conclusion

As is so often agreed, well-conducted, adequately powered, randomised trials are needed to resolve the controversy. Dr Cooper suggested that the ideal albumin versus crystalloid study would have the following features:

* A primary end point of mortality
* Randomised and blinded with baseline equivalence and minimal bias
* Very large - up to 7000 patients to have adequate statistical power
* Albumin would be given for resuscitation, not to supplement albumin levels
* Pre-load would be optimised and equalised, if possible, in the study groups

This are the principles underlying the Australia and New Zealand Intensive Care Society Clinical Trials Group Study funded by the National Medical Research Council. This will be conducted in patients already in intensive care, not pre-hospital or in emergency situations or the operating room. There will be no cardiac surgery patients because their baseline mortality is low and to detect a difference between treatments would be virtually impossible. Burns patients are also excluded because it was felt the topic was too controversial for investigation to be undertaken adequately. This study will commence recruitment in July 2001 and will run over the next two years.

Tom Stewart (Canada) discussed the current practice in Canada with respect to intravenous fluid use. When the BMJ meta-analyses were published, these had a major impact in Canada on attitudes to and use of albumin, with - in effect - an official warning to avoid the use of albumin. It was decided to investigate what drives the choice for colloids and, if colloid rather than crystalloid was chosen, why a synthetic colloid would be chosen over a natural colloid such as albumin. The study was supported by an albumin supplier.

In the qualitative phase of this study, expert panels of fluid users in variety of therapeutic areas were consulted during focus groups across the Toronto region, conducted by a specialist organisation, and five one-on-one interviews were conducted for specialists whose area of expertise did not fit with the focus group sessions.

The quantitative phase employed a 61-question survey that had been tested with the expert panel. The objective was to survey 10% of fluid users in Ontario, Canada's largest province. This representative 10%, across all specialities were selected randomly from the central physician register database, although all cardiac surgeons and paediatric intensivists were surveyed, because of their small numbers. In addition, general practitioners with hospital associated-practices and general internists who use fluids were included. Those surveyed received an honorarium and were called to remind them to complete the questionnaire. Response rate was around 70% across the three groups.

The questions covered the topics of
* Demographics
* Usual intravenous fluid practice
* Use of fluids in specific clinical conditions
* What factors influenced decision on fluid use

The majority of responders dealt with adults rather than children, were aged around mid-40s with a large predominance of males; 63% reported using albumin in the last year and 55% had used a pentastarch preparation, with use of small amounts of other colloids and blood products. During the previous year, around 25% of respondents reported 100% crystalloid use and 45% reported 90% crystalloid with 10% colloid use. These were grouped as high crystalloid users, and the remaining respondents as non-high crystalloid users. There was a significant correlation between any work in intensive care and non-high crystalloid use. Estimating the use of synthetic colloid rather than albumin, the results showed polarisation of usage; 14.8% used only synthetic colloid and 27% used only albumin. 'High synthetic' users were those working in anaesthesia and adult critical care. 'High albumin' users were in paediatric critical care, respiratory medicine, nephrology, internal medicine and GPs.

Factors influencing decision making for crystalloids.	Factors influencing decision making for colloids
Lower purchase cost 'Replaced what the patient needs most' Little or no side effects Little risk of transfer of infection	Want to manipulate patients' oncotic pressure Use for patients with large volume blood loss

Table 1 Factors influencing the decision to use crystalloid or colloid

Factors influencing the decision to use crystalloid or colloid are summarised in Table 1.

Considering the factors influencing the choice of synthetic colloids or non-synthetic colloids:

* Responders professed that having to acquire albumin from, for example, blood banks, did not influence their decision to use it.
* No respondent felt any particular feature to be important or not important in making his or her choice, including cost.
* High albumin users professed, more frequently, not to be aware of any literature comparisons with pentastarch showing superiority of the latter.

Clinical situations where albumin would be the fluid of choice for more than 50% of responders are listed in Box 3.

* Burn patients after 24 hours
* The very oedematous patient
* Severe ascites
* Hypoalbuminaemia
* Large volume paracentesis

Box 3 Clinical scenarios (of 13 suggested) where albumin was the fluid of choice for more than half the responders

For pentastarch, there were no specific scenarios where the majority of doctors would prefer to use it. Thus, albumin appeared to have more identified clinical niches.

Professor Stewart was concerned that the use of pentastarch appeared to be related to marketing visits, rather than on the basis of evidence. Similarly, one third of those specialists in anaesthesia, adult and paediatric critical care and nephrology, said that personal feeling influenced their choice to give colloid, rather than evidence. The key findings in this study of fluid usage in the Ontario area are summarised in Box 4.

* A high ratio of colloid use in critical care
* Two distinct groups of colloid users - those who choose synthetic and those who chose albumin
* Albumin users are uncertain of the literature
* More identified clinical niches, in Ontario, for albumin use
* Marketing and personal feeling play a large role in selection
* The majority of responders felt they needed more evidence

Box 4 Key findings of a study on intravenous fluid usage in the Ontario area

Professor Stewart concluded that, rather than critique the comparisons that have been made, studies should be conducted to provide the evidence that people require.

The formulation of albumin solutions

If, as has been frequently discussed on the basis of published meta-analyses, there is no major evidence that albumin is beneficial in terms of outcome and, perhaps, some evidence that it may be deleterious, mechanisms should be examined to determine if there are any reasons why albumin might be deleterious to patients.

Albumin itself is physiological and probably safe for patients, but Elliott Bennett-Guerrero (USA) suggested that the vehicles in which albumin solutions are formulated are not physiological, are possibly unsafe and may account, in part, for some of the worse outcomes found in trials.

Considering the solutions frequently used for intravenous fluid resuscitation:

* Electrolytes - 0 .9% (normal) saline does not contain other electrolytes that may be important, for example, acetate or lactate which are converted to carbonate and help avoid metabolic acidosis during surgery.
* Ringer's Lactate (RL)/ Hartmann's solution, Plasma-Lyte - are balanced solutions, containing acetate or lactate.
* Human albumin 5% solution,

usually contains sodium and chloride and no significant quantities of other electrolytes and is considered expensive.

* 6% hetastarch in a normal saline-type vehicle has been used for many years but controversy surrounds its impact on bleeding and other clinical parameters.
* Hetastarch in a balanced-type solution is the first approved starch fluid to be formulated in a more physiological vehicle.

Dr Bennett-Guerrero suggested that the vehicle for albumin, that is saline solution, may have an impact on renal function. Animal work conducted some 20 years ago showed that normal saline-based fluids led to hyperchloraemia, which produced a progressive renal constriction and a fall in glomerular filtration rate. The changes in renal blood flow correlated with plasma chloride levels. In a study of volunteers who received saline or RL solution, those receiving saline had more hyperchloraemic metabolic acidosis and a significant delay in the time to first urination than the subjects receiving RL. In 24 patients undergoing genitourinary surgery, who received saline or RL, there was more hyperchloraemic metabolic acidosis in those receiving saline. This study was not powered to study renal function, but Dr Bennett-Guerrero observed a trend to lower renal output in those randomised to normal saline.

This consistency suggests that this is a real effect of normal saline-based preparations.

A randomised clinical trial is in progress in patient undergoing cardiac arterial bypass grafts, and/or valve surgery, who have been randomised to RL, albumin, hetastarch in normal saline or hetastarch in a balanced electrolyte vehicle. Interim analysis of renal function in 100 patients has shown the two balanced electrolyte preparations to be associated with higher urine output in the 4 hours after surgery than the two normal saline-based preparations. Creatinine levels on post-operative day 2, were increased in patients receiving normal saline-based solutions, but not in those receiving balanced electrolyte-based preparations. The differences in serum creatinine were maintained to the seventh post-operative day. Of 200 patients randomised, six required renal dialysis after surgery, all having received normal saline-based preparations.

Dr Bennett-Guerrero concluded that there is increasing evidence that the administration of albumin, and of other normal saline-based solutions, can result in worsening in renal function and may be the cause of excess mortality apparently observed in some studies. Balanced fluids are superior to normal saline-based fluids with regard to renal function.

What is the place for albumin?

Marc-Jacques Dubois (Belgium) addressed this tricky question and tried to review the data that justify the use albumin in critically ill patients, his own speciality. He presented a list of the features of albumin that should be considered (Box 5).

* Maintenance of colloid osmotic pressure
* Anti-oxidant and free-radical scavenger functions
* Apoptosis regulation
* Maintenance of microcirculatory integrity
* Effects on coagulation
* Binding of endogenous and exogenous substances
* Efficacy in reaching a haemodynamic goal
* Less oedema formation
* Possible reduction in complications of surgery such as wound healing and decubitus ulcers
* Anti-inflammatory effects
* Maintenance of the acid-base state
* Effects on the myocardium
* Use in particular clinical situations - for example spontaneous bacterial peritonitis

Box 5 Features of albumin

Whilst some of these properties are potentially clinically useful, they are not immediately relevant to the use of albumin as a resuscitation fluid. Is there clinical evidence to justify the use of albumin? Dr Dubois found it difficult to say 'yes' without expressing concerns. Those who would reply 'no' would suggest some of the properties of albumin as being deleterious in some specific situations and cite the Cochrane Group meta-analyses. However, heterogeneity of study populations, inclusion of neonates, cancer patients and those not critically ill, variations in the severity of the disease, poor

quality of the primary studies are all good grounds for criticism of a study that purported to investigate the use of albumin in critically ill patients. Whatever the criticisms of the Cochrane Group's analyses, they have given the spur to re-examine the use of albumin and to question or justify current practice. The meta-analysis presented as a poster at the congress by Wilkes and Navickis (see p X) is interesting because it includes 42 trials that include mortality data and the patients were basically more sick. The effects of blinding, mortality as an endpoint, crossover and small trial bias are taken into account in this analysis and no excess mortality is demonstrated in the albumin recipients. It would be premature to draw a conclusion based on an abstract, and the full paper is awaited.

If the goal is to reach a specific haemodynamic endpoint, to simply raise the blood pressure, to try to reach a specific filling pressure, there are alternatives to albumin, including crystalloids. Albumin should be looked at as, perhaps, a means of preventing or improving organ dysfunction. Dr Dubois suggested that there should be a move away from the thinking that albumin is a resuscitative fluid, and towards greater consideration of its other properties.

Results of randomised studies with adequate statistical power, such as those mentioned by Dr Cooper and a study about to start in Brussels should provide less controversial evidence on which to base informed opinions on the relative merits of crystalloids and colloids in specific situations.

This publication is produced with the aid of an unrestricted educational grant from
The Plasma Protein Therapeutics Association Europe
Boulevard Brand Whitlock 114/5
1200 Brussels Belgium
June 2001

21st International Symposium on Intensive Care and Emergency Medicine
Intravenous Fluids 1

PPTA EUROPE
Plasma Protein Therapeutics Association