Burns resuscitation: what place albumin?

Keith Judkins

The Cochrane analysis of the use of albumin in critical illness has highlighted the need for more well-conducted studies on colloid use in burns. The lack of objectivity in the press regarding this material has compromised our ability to deliver those studies. The analysis provides no evidence that albumin is unsafe for the initial resuscitation of uncomplicated burns, and the fall in its use is more likely to be cost-related.

There has been much discussion in the past year or so about the clinical use of human albumin solutions, following publication of the Cochrane Collaboration's report on their use in the critically ill (Cochrane Injuries Group Albumin Reviewers, 1998). The issues raised have included the validity of meta-analysis as the foundation of evidence-based medicine, the perceived flaws in study selection for this analysis (Horsey, 1999), the wisdom and timing of the release of the report to the media, and the relevance of this particular review to the real clinical situations in which albumin has been used (Correspondence, 1998).

The publicity accompanying the report's publication was much criticized. An embargoed press release stimulated a brief flurry of media interest. Pieces were written in the *Independent* (Laurence, 1998) among others, and the term 'killer albumin' was used at least once by the tabloid papers. Clinicians faced next day, as this author was, by the parents of a child with a scald saying 'You aren't going to give him the killer fluid, are you, Doc?', could be forgiven for being personally offended by the manner in which this issue was handled. However, these things tend to be one-day wonders; the public loses interest quickly, unless someone can be identified who has died as a direct result of the treatment described in the study; a story without human interest tends not to run.

The subsequent months have allowed time for reflection and debate. The Cochrane Group express periodic concern about what they deem lack of action by the Medicines Control Agency (MCA) (Boseley, 1999), and non-medical health journals write admiringly of their work (Watts, 1999). Three facts remain:

1. The report was published, raising questions about the safe use of albumin in the critically ill that merit serious consideration
2. The public must be assured that products used for their treatment are as safe as possible; vigorous, objective investigation of any doubt raised about a product's safety must be undertaken (Margarson and Soni, 1998)
3. The climate in which these two issues can be addressed in respect of albumin has deteriorated markedly as a result of intemperate remarks made to the media and in the medical press by the authors.

This paper will look at the Cochrane report's findings so far as they apply to burn care, and attempt to define a way forward for burns resuscitation.

A BRIEF HISTORY OF FLUID RESUSCITATION IN BURNS

Before World War II, most burns victims with more than 20% body surface area burned (%tbsa) were at mortal risk from acute renal failure. Fluid infusion was used but was ill defined until the early 1950s, when several groups of workers (e.g. Evans et al, 1952) devised formulae to guide resuscitation. To cut a long and complex story short, this culminated in the derivation of the Parkland (or Baxter) formula in the USA, and the Mount Vernon (or Muir and Barclay) formula in the UK. It is significant to this review that:

1. Neither formula was ever subjected to randomized controlled study or published as an original paper in a peer-review journal
2. Both formulae were arrived at by retrospective analysis of large numbers of successfully resuscitated patients.

Burns patients who used to die before fluid resuscitation was used no longer died. The practi-

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tioners of the day deemed the matter so self-evident it needed no further elucidation. Renal failure and consequent death were avoidable unless systemic sepsis and multi-organ failure intervened. Successful treatment of the latter would await development of modern intensive care 20 or so years later, and even now prognosis is poor.

Since then, many thousands of patients have undergone fluid resuscitation using either crystalloids or colloids or, most often, various combinations of both. Only a small proportion have died; most owe their lives to prompt fluid resuscitation, and until the early 1980s no significant differences were discernible between burn mortalities in the UK (colloid-based resuscitation) and the USA (crystalloid-based resuscitation). Death during resuscitation is now a very rare event, most deaths are associated with late septic complications, and the greatest reduction in mortality in recent years has occurred in patients under 40 years of age since the advent of aggressive early surgery to remove the burn wound (Ryan et al, 1998).

THE PATHOPHYSIOLOGICAL PROCESS

Initially, various substances are released from damaged tissue, including lipoprotein complexes, through an array of mediators. These substances trigger the extrusion of white blood cells through the capillary endothelium. This causes protein to leak into the interstitium, a process teleologically designed to scavenge damaged tissues and initiate local wound healing. Capillary permeability increases temporarily, and fluid follows the leaking proteins so that oedema forms. Capillary dilatation maximizes blood flow to the injured part. The cellular mechanisms that facilitate this reaction are complicated, and will not be discussed here.

In small burns, the reaction is entirely local. In moderate injuries, the reaction is local but on a scale sufficient to cause a significant reduction in circulating volume. The early work on fluid resuscitation determined that patients with burns greater than 15% tbsa were at risk of renal failure, and therefore fluid resuscitation was needed. Because of differences in fluid handling and in surface area to weight ratio, children get into difficulty at a lower %tbsa burn than adults, so for children the trigger for fluid is accepted as 10% tbsa.

In major burns of 40% tbsa or more, the 'dose' of inflammatory mediators entering the circulation may be sufficient to trigger the systemic inflammatory response syndrome (SIRS). Inhalation injury or multiple injuries greatly increase the risk of SIRS and significantly increase mortality, especially if complicated by sepsis (Ryan et al, 1998).

THE BASIS OF FLUID RESUSCITATION

The clinical presentation is the result of an intense tissue reaction to injury, leading to a transient capillary leak which recovers exponentially over about 24 hours and peaks between 3 and 6 hours post-burn. It is proportional to the interface between injured and normal tissue, i.e. to body surface area burned. The time to significant fluid loss is 1–4 hours, depending on burn size, not minutes as in shock resulting from haemorrhage. The goal of burn resuscitation is therefore to anticipate and prevent shock, not simply to treat it. Urine flow remains the best index of adequate resuscitation in most patients. Patients with major burns and/or smoke inhalation are a different matter.

Capillary leak allows proteins to enter the extracellular compartment, as has been understood for many years (Sørensen and Sejrsen, 1965). The dynamics of the physiological changes that follow burn injury were extensively studied, culminating in a thorough review by Davies (1982). The most osmotically active substance in this circumstance is sodium, the most plentiful particle in solution. With capillary integrity impaired, plasma proteins no longer exert their osmotic effect; further leak of fluid into oedematous areas is therefore promoted until capillary integrity returns to normal. Fluid therapy should support circulating volume sufficient to maintain flow to vital organs, but excessive fluid will exacerbate oedema further (Clark et al, 1988) regardless of type of fluid used. The effect of over-resuscitation on organ function has not been investigated, but logic suggests it would be detrimental. The published literature hints towards this, but hard evidence is lacking.

The kidneys and their supporting hormonal systems respond sensitively to changes in circulating volume, more so than any other organ except, arguably, the gut. Release of hormones that conserve sodium and water occurs early after burn injury, even if resuscitation is started promptly. The body cannot therefore respond to an excess water load, so it is important that water given is sufficient only to balance the sodium administered and to support metabolic needs. Very hypotonic solutions are therefore inappropriate. Ringer's Lactate (Hartmann's) solution is slightly hypotonic and therefore delivers enough metabolic water for daily needs as well as achieving resuscitation. Children have higher metabolic water needs than adults as a result of greater evaporative losses, so they always need extra metabolic water at 1500 ml/m^2 body surface per day. Plasma protein solutions are isotonic for sodium so extra metabolic water is needed at normal maintenance rates. The two commonly used formulae are given in *Table 1*.

THE COCHRANE STUDY IN THE BURNS CONTEXT

The Cochrane analysis cannot reasonably be criticized on the basis of its statistical methodology, which is robust, but the selection of papers for analysis was less satisfactory, because it lumped together all three approved indications for use of albumin: burns, hypoproteinaemia and hypovolaemia. The heterogeneous case mix represented by the individual papers could not possibly be appreciated by the authors, who do not practice in intensive care or burns (Frame and Moiemem, 1998). This alone is sufficient to cast doubt on their conclusions.

The Cochrane analysis included only three papers on burnt patients. The first (Jelenko et al, 1979) was 19 years old at the time of the Cochrane study, and described an experiment in which hypotonic fluid (Hartmann's, sodium 130 mmol/litre) was compared with hypertonic saline (240 mmol/litre) and with 1.25% albumin in hypertonic saline. The albumin group fared better in the short term, but there were less than 10 patients in each group, the incidence of inhalation injury was high and sepsis rates differed markedly between groups. Extreme caution is needed when interpreting this study, the results of which have never been implemented in routine practice.

The second (Goodwin et al, 1983) also tinkers with standard resuscitation protocols, by addition of 2.5% albumin in one group in the first 24 hours. Both groups received albumin in the second 24 hours, in accordance with the Parkland protocol. The interesting finding in this study was the effect on extravascular lung water in the week following resuscitation: fluid accumulated in the lung in patients given early albumin, but not in those in whom albumin was withheld until day two.

The third (Greenhalgh et al, 1995) is a hypoalbuminaemia study which happens to have been conducted in burnt patients. It clearly showed that, although hypoalbuminaemia is a useful prognostic indicator, giving albumin does not improve the prognosis in paediatric patients. Other work confirms this finding (Sheridan et al, 1997). Two points are worth noting:

1. All patients received albumin during resuscitation, which was guided by the Parkland formula
2. If serum albumin dropped below 10 g/litre, the protocol included the option of giving albumin at this point.

SO, WHAT PLACE ALBUMIN?

1. Most burns patients are not critically ill. The goal of fluid resuscitation is to prevent patients becoming critically ill. The overwhelming evidence from the many thousands of patients who have been given albumin for resuscitation is that it does no harm in this context
2. Hypoalbuminaemia is not an appropriate indication for albumin administration in critical illness, including burns
3. Colloid solutions may exacerbate organ, especially lung, failure in some circumstances. There is no reason to believe this caveat applies only to albumin
4. If there is a problem, the villain is not shown to be albumin.

There is nothing new here. Sensible doctors have heeded the evidence and have long given up using albumin to treat a low blood level of albumin. Doctors using the Mount Vernon formula are questioning whether albumin solutions contribute sufficient added value to justify their much greater cost and some have changed to crystalloid-based resuscitation. Small wonder that the use of albumin in the UK has declined, but this is on grounds of cost or lack of efficacy, not clinical danger. It should be noted that there is some evidence of morbidity with crystalloid-based resuscitation (BA Pruitt, personal communication, 1999; Deb et al, 1999), which is not seen when colloids are used.

The Cochrane study and the previous, less publicized analysis comparing crystalloids with colloids (Schierhout and Roberts, 1998) have pinpointed the need for carefully designed studies in the critically ill. Neither study demonstrated whether colloids themselves are harmful, or whether the increased mortality shown is the result of patient selection, volumes or doses adminis-

TABLE 1.
Commonly used burns resuscitation formulae

Formula title	First 24 hours	Second 24 hours
Mount Vernon (Muir and Barclay)	Plasma at 0.5 ml/kg per % tbsa during each period after injury (periods: 4,4,4,6,6 hours)	Plasma at 0.5ml/kg per %tbsa over 12 hours, maintenance fluid thereafter
	Basal metabolic water at standard rates, as dextrose 5%	
Parkland (Baxter)	4 ml/kg per %tbsa, half in first 8 hours, half in second 16 hours, from time of injury	2ml/kg per %tbsa plus 0.5ml/kg per %tbsa of 5% albumin

%tbsa = percentage of total body surface area burned. N.B. Both formulae are derived from retrospective analysis of successful fluid resuscitation in large numbers of patients. Neither formula should be followed slavishly. They identify a starting point; the rate should be adjusted over time according to clinical and other monitoring

tered, inadequacies in monitoring the effect, or other factors. The questions raised far outnumber the answers supplied. The subsequent denigration of albumin cannot be justified by this analysis, and the MCA were right to conclude that:

> **'there is insufficient evidence of harm to warrant withdrawal of albumin products from the market' (Woodman, 1999).**

More controlled studies to determine the appropriateness of colloid use in burns (Childs, 1998) and in critical care (Chalmers, 1998) are undoubtedly needed. But critical illness is a complex entity, so studies must address the indications for colloids, the criteria for patient selection, the specific effects of different types of colloids, the effects of the concentrations in which they are administered, the effects of any carrier fluids, and the best ways to monitor their effects. Measuring colloid osmotic pressure is an attractive idea for guiding therapy but has yielded indifferent results so far when used as a prognostic indicator (Blunt et al, 1998).

Unfortunately, our freedom to conduct such studies, especially in respect of albumin, has been damaged by the statement of the Director of the UK Cochrane Collaboration that:

> **'If I survived, I would attempt to sue anyone who had given me an infusion of albumin; and I would not give my informed consent to take part in a randomised trial' (Chalmers, 1998).**

This comment is rich, coming from one who in the same letter urges:

> **'those working in intensive care [to acknowledge] the need for reliable evidence about the effects of their care on outcomes that matter to patients.'**

There is no doubt in my mind that albumin is inherently safe and should be studied alongside other solutions in critical illness, in spite of Dr Chalmers' comments. It can be given safely in burns patients when appropriate, in accordance with the new guidance issued by the MCA (Woodman, 1999). The MCA Expert Working Party recommended that the indication for albumin solutions should focus on replacement of lost fluids, that administration should be closely monitored particularly for cardiovascular effects, and that treatment of hypoproteinaemia and burns are no longer appropriate indications per se. It is right to weigh the cost-benefit relationship when using albumin, but cost alone should not deter use of albumin if it is clinically indicated.

The Cochrane analysis has clearly shown the need for more well-conducted studies on colloid use in burns. We knew that already (Blunt et al, 1998; Childs, 1998). The intemperate remarks by Cochrane personnel in the media and the medical press have seriously compromised our ability to deliver those studies. Let us hope that this effect is short term. **HM**

Conflict of interest: none

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KEY POINTS

- The Cochrane group have raised concerns over albumin, and its use in burns has subsequently been questioned.
- Burns resuscitation formulae are supported by a wealth of clinical experience.
- The burns papers in the Cochrane study are too few and too heterogeneous to allow firm conclusions to be drawn in respect of the burns population.
- Use of colloids in massive burns or smoke inhalation injury requires great care.
- Albumin use should be carefully monitored, particularly for cardiovascular effects.
- More studies are needed on the use of colloids in major burns.