Albumin in meningococcal disease

The management of acute meningococcal disease (MD) exemplifies what is best and worst about modern paediatric intensive care. The best because, in the face of well-staffed teams with centralized experience, survival has improved dramatically (clinical scoring systems such as the Glasgow Meningococcal Septicaemia Prognostic Score indicate that for the highest risk patients (score >12) the mortality has fallen from 100% (Thomson et al, 1991) to 37% (unpublished data, Peters et al, 2000)). The worst because there are no randomized trial data supporting many widely used interventions. This has caused problems in recent years as enthusiasts for novel therapies suggest that trials are now unethical because of improved outcome (Smith et al, 1997), while across the board outcomes are better than previously.

IMMEDIATE MANAGEMENT

The immediate management of any critically ill child should follow the principles of airway, breathing and circulation in addition to specific therapy. In acute MD, support of the circulation is often the most pressing issue. The combination of myocardial depression and peripheral vasodilatation mean that large volumes of fluid resuscitation are essential to optimize cardiac output and organ perfusion. The widely adopted protocols suggest the immediate administration of 20 ml/kg of normal saline or 4.5% human albumin solution (HAS) to a child in septic shock, which is then repeated if there is no response.

Cases with severe shock may require more fluid, 100–200 ml/kg in the first 12–24 hours of intensive care. A shift in emphasis from fear of pulmonary oedema to recognition of the vital importance of aggressive fluid administration has been apparent to long-serving members of our paediatric emergency transport team. It is probable that much of the improved outcome of these cases results from high quality immediate resuscitation on presentation.

USE OF ALBUMIN

In paediatric practice 4.5% HAS has been widely used as the first-line resuscitation fluid. The high molecular weight (69 kDa) and negative charge (Klein et al, 1992) are theoretical advantages which suggest that HAS should preferentially increase intravascular fluid volume in the presence of a functioning endothelial barrier. If true, this is a significant advantage over larger volume crystalloid administration in the resuscitation situation when there may be many pressing requirements for limited intravascular access (e.g. antibiotics, coagulation factors or inotropes).

COCHRANE META-ANALYSIS

In 1998 the Cochrane Injuries Group Albumin Reviewers published a meta-analysis of the use of HAS for a variety of indications in critically ill patients. They suggested an increased mortality of 6% in comparison to a variety of control fluid regimens (Cochrane Injuries Group Albumin Reviewers, 1998). The proposed mechanism for the excessive mortality was increased interstitial fluid and particularly pulmonary oedema.

This study has been widely criticized for several reasons, particularly the heterogeneity of the trials included. These address the use of varying concentrations of HAS to achieve a range of clinical endpoints in hypovolaemia, burns or hypoproteinaemia. One recent editorial suggests that:

'combining aspirin studies for eclampsia...stroke...and myocardial infarction, would be analogous to the albumin meta-analysis' (Drummond and Ludlam, 1999).

RELEVANCE TO ACUTE SEPSIS

This criticism may be particularly relevant to the choice of resuscitation fluid in acute sepsis. Only one study of 17 patients investigated HAS administration in sepsis (although cases of trauma were also included) and this showed a non-significant fall in mortality with HAS administration.

The largest study of HAS administration (107 patients) for hypovolaemia as part of 'vascular leak syndrome' recorded no deaths in control or treatment groups, which is not consistent with an excess mortality of 6% caused by HAS. The possibility that HAS may be useful in resuscitation of cases with dysfunctional endothelium is therefore not addressed by this review. The suggestion that pulmonary oedema might be a cause of excess mortality attributable to HAS also does not 'ring true' with clinicians. The severity of respiratory failure has little impact on outcome in paediatric intensive care (Nadel et al, 1998; Peters et al, 1998).

It is not surprising therefore that many clinicians find these data of much improved outcome and significant risk with a mainstay of fluid management difficult to reconcile. However, there is no evidence that HAS does any good and now there is a strong suggestion that it may do harm. The Cochrane group do not overstate their conclusions and only suggest that 'the use of albumin in critically ill patients should be reviewed'. This has been undertaken by a Committee on the Safety of Medicines expert working party who concluded recently that there was 'insufficient evidence of harm to warrant withdrawal of HAS,

and that the effect on mortality will only be answered by large randomised controlled clinical trials'.

FUTURE TRIALS

Discussions are underway between paediatric intensive care clinicians throughout the country, exploring the possibility of a large multicentre randomized controlled trial of crystalloid, HAS, or synthetic colloid as resuscitation fluid in in critically ill children following cardiac bypass and acute sepsis. Planned recruitment of 2–3000 cases suggests that paediatric intensive care may be moving rapidly in the direction of quality evidence-based practice.

The Cochrane group should be commended for the initiative to challenge this long established and unproven therapy. Inevitable conclusions were drawn by some observers which blurred the genuine issue. However, the effect of this widespread debate may be something much more important than the correct choice of fluid for initial resuscitation — a framework for ambitious high quality trials to determine best practice in paediatric intensive care. We may soon be able to know rather than feel what is best for our patients with meningococcal septicaemia. HM

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KEY POINTS

- The mortality from meningococcal septicaemia is falling with the increased availability of specialist paediatric intensive care facilities.
- An essential part of early resuscitation of the child with septic shock is rapid administration of large volumes of intravenous fluid.
- The improvement in outcome from meningococcal disease has been achieved predominantly with the use of 4.5% human albumin solution.
- Fear of pulmonary oedema should not lead to undertreatment of hypovolaemia. Pulmonary oedema is a frequent feature of meningococcal disease but is an extremely rare cause of mortality.
- Human albumin solution has no proven advantage over other resuscitation fluids, is expensive and carries an infection risk. Direct associations with increased mortality are unproven.
- The choice of fluid is likely to be less important than manner in which it is used. Optimal fluid management in shock is determined by continuous central venous or left atrial pressure monitoring.

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