Volume Replacement in Dengue Shock Syndrome

by

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Abstract

The treatment of dengue shock syndrome (DSS) is a medical emergency. Prompt and vigorous volume replacement therapy is required, with extreme care to avoid fluid overload. Recognition of the importance of increased vascular permeability in the pathophysiology of DSS and of the critical need for parenteral fluids in resuscitation has had a dramatic effect on mortality from the disease over the last 40 years. However, until recently there has been little research to determine the optimal fluid regimen, and the choice of fluid has remained largely empirical. Colloid and crystalloid fluids have different physicochemical properties which influence the patterns of distribution and elimination, as well as the secondary osmotic effects. In two recent double-blind randomized trials in Viet Nam, initial resuscitation with colloid fluids (dextran 70 or 3% gelatin) restored cardiac index and pulse pressure and normalized haematocrit more quickly than either of the crystalloid fluids (physiological saline or Ringer’s lactate). There was no difference, however, in the overall recovery time or the subsequent requirement for fluids. From the larger study it was apparent that the major determinant of clinical response was the width of the pulse pressure at presentation with shock, the small number of children with pulse pressures of ≤ 10 mm Hg requiring significantly more resuscitation than those with higher pulse pressures. Within this more compromised group there was a trend to earlier, sustained recovery among those who received one of the colloids. It appears that the majority of children with DSS recover with timely infusion of crystalloid fluids alone, but that an important minority may benefit from initial resuscitation with a colloid. Large trials will be necessary to confirm this effect and to clearly characterize the subgroup of children who might benefit from initial colloid therapy. Given the huge burden of dengue disease in South-East Asia, if a true benefit is established in a subgroup of patients, this may have a significant influence on mortality in the region.

Keywords: Dengue shock syndrome, medical emergency, volume replacement, resuscitation.

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**Introduction**

Infection with dengue virus is one of the leading causes of illness and hospital admission of children in South-East Asia (1,2). Infection may be asymptomatic, or may result in a variety of clinical syndromes ranging from dengue fever (DF), a non-specific febrile illness, to dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). The pathognomonic feature differentiating DHF from DF is an increase in vascular permeability resulting in the leakage of plasma from the intravascular compartment to the extravascular space (3,4).

In severe DHF the loss of plasma is critical, the patient becomes hypovolaemic, exhibits signs of circulatory compromise, and may progress to profound shock.

The management of established DSS involves immediate resuscitation with parenteral fluids, with the intention of restoring and maintaining adequate circulation during the period of increased vascular permeability. Particular care is required to try to avoid fluid overload with all its complications, especially in settings without access to sophisticated intensive care facilities. If appropriate fluid resuscitation is started at an early stage, shock is usually reversible, and once the capillary leak has been resolved, most patients recover rapidly. The current recommendation from the World Health Organization (WHO) (5) is for initial volume replacement with crystalloid solutions, followed by plasma or colloid solutions for those patients with profound or refractory shock.

**Normal fluid balance and the crystalloid/colloid debate**

For many years there has been a controversy regarding the use of crystalloid or colloid solutions for the emergency management of hypovolaemic shock, irrespective of the underlying disease process (6,7,8). Total body water is distributed between three main fluid compartments in the body. Intracellular fluid makes up approximately two-thirds of the whole, with the remaining one-third, the extracellular fluid, being distributed between the intravascular (25%) and interstitial compartments (75%) [Figure 1].
Thus, only 25% of the one-third of the total body fluid (8%) contributes to the normal circulating blood volume. The intracellular fluid is separated from the extracellular fluid by a selective cell membrane that is highly permeable to water, but not to most of the electrolytes or proteins in the body. Within the extracellular compartment however, the intravascular and interstitial fluids communicate continuously through the pores of the endothelial membrane, which are highly permeable to almost all solutes except proteins. Parenterally-administered fluids distribute rapidly throughout the three fluid compartments - intravascular, interstitial and intracellular, according to specific physicochemical properties of the individual solutions. The proportion of the fluid remaining within the intravascular space is one of the major determinants of the effectiveness of a given fluid for volume resuscitation.

Broadly speaking, isotonic crystalloid solutions distribute equally between the intravascular and interstitial compartments but do not enter the intracellular compartment. In contrast, a proportion of all hypotonic crystalloid solutions, determined largely by the content of the major extracellular ion, sodium, passes quickly into the intracellular compartment, and the volume left within the intravascular compartment may be minimal. Thus, one litre of physiological saline administered parenterally to a healthy person will distribute throughout the extracellular fluid space to maintain normal osmolality, with 25% (250 ml) remaining within the intravascular space and 75% passing to the interstitial space within a few minutes. In contrast, one litre of 5% dextrose, which contains no sodium and can thus be regarded effectively as free water, will distribute equally throughout all the three fluid compartments to maintain normal osmolality, but in this case only 25% of the one-third of the total volume, that is approximately 80 ml of fluid, will remain within the intravascular compartment. For this reason hypotonic crystalloid solutions should never be used in situations where the restoration of the circulating blood volume is a priority.

Theoretically, colloid solutions offer advantages over crystalloid solutions for emergency resuscitation. Firstly, the immediate distribution is primarily within the intravascular compartment limited by the permeability of the endothelial barrier. Secondly, the colloid molecules increase plasma oncotic pressure thereby altering the balance of fluid flux across the endothelium and drawing fluid back into the intravascular compartment from the interstitial space. Thus, in contrast to crystalloid solutions, a bolus of a colloid solution provides volume expansion over and above the actual volume of fluid infused. All synthetic colloids are polydisperse, with a range of molecules of different molecular weights in one solution. The magnitude of the effect on plasma oncotic pressure is determined by the average molecular weight of the colloid molecules; small molecules exert a relatively greater osmotic effect than larger molecules at the same concentration. However, large molecules remain within circulation longer than small molecules, which are rapidly excreted by the kidneys or may be lost from circulation by leakage across the endothelium. Thus, for example, 6% dextran...
70 (average molecular weight 70,000 Daltons) and 6% hydroxyethyl starch (average molecular weight 200,000 Daltons) provide volume expansion for at least 6-8 hours, whilst 4% gelatin solutions, consisting of molecules of considerably smaller average molecular weight (35,000 Daltons), remain effective for only 2-3 hours\(^9\). There is, however, a concern particular to patients with increased vascular permeability, that colloid molecules may themselves leak into the interstitium and exert a reverse osmotic effect, thereby drawing out intravascular fluid and worsening the situation\(^10\).

Another significant determinant of the effect of a colloid infusion is the concentration of the solution. Hyperoncotic solutions, such as 10% Dextran 40, have considerably greater ability to draw fluid back into the intravascular compartment than isoncotic preparations of the same molecule. However, there are major concerns about the safety of hyperoncotic solutions, especially in hypovolaemic patients, in whom there is a real risk of developing acute renal failure\(^11,12\). Other concerns relating to the use of colloid solutions include the potential for allergic reactions and the established adverse effects on blood coagulation\(^10\). Crystalloid solutions are generally safe, reaction free, and have only dilutional effects on coagulation.

**Fluid trials in dengue shock syndrome**

Thus, it is apparent that the choice of fluid for resuscitation of hypovolaemic shock is not straightforward. However, despite the importance of the question there have been only two randomized and blinded clinical trials, published in international literature, that have attempted to investigate the impact of different fluid regimens in the initial resuscitation of DSS\(^13,14\). The first study\(^13\), a pilot involving 50 children with DSS, was not designed to answer definitively the question of colloid versus crystalloid. However, the trial did demonstrate that there were important differences in the immediate clinical response to different fluid regimens, with significantly greater improvements in surrogate markers of recovery such as cardiac index, hematocrit and pulse pressure among children who received a colloid rather than a crystalloid at first presentation. All the children recovered fully with fluid management alone, and there were no differences in overall time to recovery or total fluid requirements.

The second study, conducted over a one-year period in a single hospital, recruited 230 children with DSS who received one of four different fluids, two crystalloids and two colloids, for initial resuscitation\(^14\). The most significant factor predicting the clinical response to resuscitation was the width of the pulse pressure at presentation. Children with a pulse pressure of \(< 10 \text{ mm Hg}\) on admission were both more likely to suffer prolonged shock and to experience subsequent episodes of shock than those presenting with higher pulse pressures. Although few clear differences in outcome were demonstrable between the recipients of the four different fluids, it was apparent that the subgroup with the lowest pulse pressures at presentation improved significantly more quickly if they received one of the colloids, whereas in the children presenting with
higher pulse pressures there was no difference in the outcome between the groups. This suggests that most children with DSS can be effectively managed with crystalloid fluids alone, but that early treatment with colloids may improve the outcome in the important minority with very severe shock.

**Conclusion**

At present the WHO guidelines still include hypotonic crystalloid solutions among those recommended for the initial resuscitation of children with shock\(^1\). This is not appropriate, and solutions such as half-strength physiological saline or 5% dextrose diluted in physiological saline should not be recommended. If a crystalloid is used it should be isotonic (e.g. physiological saline or lactated Ringer’s/Hartmann’s solutions). Accepting this, perhaps the most important question that needs to be addressed is whether a colloid is better than a crystalloid for primary resuscitation, and if so, in what particular circumstances. If a true benefit from colloid resuscitation is demonstrable, particularly in the most compromised children, the next question is, which of the many synthetic colloid preparations currently available would be the most appropriate. Dextran solutions, originally developed in the 1950’s among the first of the synthetic colloids, are suggested in the WHO guidelines and are widely used in the management of DSS in Asia. However, for volume replacement in Europe and America, dextrans have been largely replaced by newer synthetic colloids such as hydroxyethyl starch (HES) and gelatin solutions. In particular hyperoncotic solutions such as 10% dextran 40, are no longer recommended for use in hypovolaemic patients.

Large well-designed intervention trials, properly randomized and blinded, will be required if we are to obtain definitive answers to these questions and provide good evidence on which to base future management guidelines. Given the current case-fatality rates of around 1% in centres experienced in the management of DSS, many thousands of children would need to be recruited for intervention trials in which mortality was the primary endpoint. The use of prospectively-defined surrogate outcome measures, while not ideal, is likely to be the most effective way of trying to address these issues, particularly if agreement can be reached among clinicians and researchers of the international dengue community as to which particular surrogates are most meaningful. As the global burden of dengue disease increases, if a true benefit from a particular fluid regimen is established even in a subgroup of patients, this may have a significant influence on overall mortality.

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**References**


