INVITED COMMENTARY

Unravelling the Enigma of Albumin in Dengue

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Plasma leakage occurs during the critical phase of dengue which lasts about 24 to 48 hours, leading to a rise in the hematocrit, pleural effusion, and ascites. This is followed by an equilibrium phase of about 8 to 12 hours before plasma reabsorption into circulation occurs. Fluid management is the cornerstone in the management of dengue. Understanding the phases of dengue and adjusting fluid therapy is crucial [1]. Overzealous administration of intravenous fluids before and after the leakage phase can lead to fluid overload which is as deleterious as the inadequate fluid resuscitation during the leakage phase [2]. The 2011 revised and expanded World Health Organization (WHO) guidelines recommend the use of intravenous fluids for at least 24 hours to meet the daily maintenance fluid required in addition to the deficit created by plasma leakage which is estimated to be 5-10% depending on the severity of shock [1]. This has also been adopted by the National Guidelines for the Clinical Management of Dengue Fever [3].

The type of fluid used for resuscitation in dengue has been an unresolved issue for decades. Evidence supports the use of crystalloids like 0.9% normal saline (NS) and ringer lactate (RL) for compensated shock in dengue. The efficacy of crystalloids has been reported to be comparable to colloids like dextran, in terms of mortality, restoration of hemodynamic parameters, and adverse effects [4]. However, WHO recommends that crystalloids should be used for profound shock as the initial fluid for resuscitation followed by colloids as the rescue fluid. Colloids are often preferred over crystalloids in the early stages of fluid overload to limit the volume of fluid required to maintain the intravascular volume. This recommendation is based on the earlier studies where colloids have shown to stabilize the hemodynamic profile faster at significantly lower resuscitation volumes [5]. These arguments have been challenged by later studies which have shown that the advantages offered by colloids are not only transient and without any mortality benefit, but are also associated with higher renal adverse effects in patients with shock [6,7]. The pathophysiology of shock in dengue is different from other shock syndromes and whether the application of such data to dengue fever remains to be established.

Albumin has been shown to have supportive benefits for the disrupted glycocalyx in septic shock and also reduces the fluid creep and abdominal compartment syndrome in severe burn shock [8,9]. Serum albumin has been evaluated as a predictor of shock and as a prognostication marker in dengue fever. Lower serum albumin during the initial four days of illness was found to be a predictor of progression to severe dengue in a large meta-analysis [10]. Despite the indirect evidence, studies evaluating therapeutic role of albumin in early phase of dengue in children is limited. Ranjith et al used albumin as the initial colloid, after the administration of 30 mL/kg of crystalloid fluid along with four other targeted interventions, and demonstrated a decreased positive fluid balance on day 1-3, less symptomatic abdominal compartment syndrome that necessitated invasive percutaneous drainage [7.7% in standard therapy plus (ST+) group vs 30% in ST group, P = 0.025], lower intubation and positive pressure ventilation requirements (18.4% in ST+ vs 53.3% in ST, P = 0.003), lower incidence of major hemorrhage and acute kidney injury, and reduced pediatric ICU stay and mortality (2.6% in ST+ group vs 26% in ST group, P = 0.004) [8]. Another recently published multicentric randomized open label trial reported a significant advantage of early 5% albumin infusion over RLin terms of lower hematocrit, higher platelet count and higher serum albumin level in adult patients. Early intervention with 5% albumin has shown superior control of vascular integrity and function compared to RL in hospitalized adults with grade I and II dengue hemorrhagic fever [11].

In this issue of *Indian Pediatrics*, Kaur et al included

children aged 2 months to 18 years with severe dengue presenting with persistent circulatory shock after 40 mL/kg of crystalloid administration in the emergency department [12]. The intervention group received 0.5-1 g/kg of 25% albumin infusion over 6 hours in addition to the WHO recommended standard therapy (ST). This was compared with the retrospective data obtained from a similar group of severe dengue patients who received the ST alone. Survival was significantly higher in the ST-plus albumin group (97.1%) than in the ST-only group (77.1%); $P = 0.043$. The need for inotropic support was significantly lower in ST-plus albumin group (60%) than ST-only group (94.3%); $P < 0.001$. The incidence of bleeding, acute kidney injury, need for diuretics and renal replacement therapy were significantly lower in children in the ST-plus albumin group than the ST-only group. There are very few studies evaluating the efficacy of 25% albumin in dengue. The study by Kaur et al has opened newer insights in the management of refractory dengue even though this requires a broader validation. The study had some selection bias inherent to its design and further randomized controlled trials are needed before albumin can be incorporated into clinical practice guidelines.

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