A hypothetical intervention to reduce plasma leakage in dengue haemorrhagic fever

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Abstract

Plasma leakage from increased vascular permeability, if left unattended, will lead to intravascular volume depletion. The ensuing tissue hypoperfusion and the consequent life-threatening complications may have a fatal outcome in dengue haemorrhagic fever (DHF). Although an accurately calculated volume of fluid infused during the critical phase of plasma leakage can prevent such an eventuality, the practical difficulties in its execution with properly-timed adjustments to the fluid infusion rate and the aggressive monitoring needed during this phase of the illness can limit the expected benefits of an exclusively fluid-based regime. An intervention to reduce plasma leakage in DHF complementing the standard fluid regime conceivably would improve the outcome. It is my hypothesis that fresh frozen plasma (FFP) by Fc receptor blockade and the associated reduction in immune-enhanced viral replication could reduce cytokine-mediated increase in vascular permeability. Additionally, albumin in FFP, by adhering to the glycocalyx, could further compromise fluid fluxes during the critical phase of DHF. However, this hypothesis needs to be tested by a randomized controlled study.

Keywords: Dengue haemorrhagic fever; Reduced plasma leakage; Intervention with fresh frozen plasma.

Introduction

The pathophysiological hallmark in dengue haemorrhagic fever (DHF) is plasma leakage. All the life-threatening complications of DHF ranging from shock, severe gastrointestinal bleeding, disseminated intravascular coagulation, hepatic failure and encephalopathy are a consequence of compromised tissue perfusion stemming from plasma leakage and the attendant intravascular volume depletion.[1] Clinical management of DHF centres around the judicious use of intravenous fluids to match the plasma leakage during this critical phase of DHF, which lasts about 24 to 48 hours, and thereby prevent the life-threatening and often fatal adverse consequences of prolonged shock. The collective experience of clinicians managing patients with dengue globally, and in Thailand in particular, has refined fluid

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The development and application of new national guidelines on the management of dengue fever (DF) and DHF by the Epidemiology Unit of the Ministry of Health, Sri Lanka, which has used inputs and expertise from a wide variety of sources, has facilitated the management of DHF. Fluid therapy in the presence of plasma leakage

The predictable benefits and prevention of morbidity and mortality due to DHF by the application of this management approach require early detection of entry into the critical phase, close monitoring during the entire phase of plasma leakage, subtle adjustments to the fluid infusion rates, and an informed choice between crystalloids (isotonic saline) and colloids (Dextran 40 and Hetastarch). For optimal benefit, such adjustments need to be correlated with the precise phase of plasma leakage to suit individual patient needs and the dynamism of plasma leakage. For instance, while Dextran 40 would be the colloid of choice when plasma leakage is at its peak, it could have an adverse impact when given towards the end of the critical phase of plasma leakage, at which stage, Hetastarch would be a better choice if a colloid is required. Dextran 40, by volume expansion, could cause fluid overloading if given towards the end of the critical phase when cessation of plasma leakage is imminent and the leaked-out fluid is getting reabsorbed. A prerequisite for the success of this therapy is the ability to detect early the entry of the patient into the critical phase of plasma leakage. This can be a challenging proposition in busy and overcrowded conditions prevailing in most developing countries, with the incidence of febrile illnesses due to a variety of causes other than dengue. Under these conditions, it is possible to falter in the critical monitoring needed to detect plasma leakage as well as apply flexibility to the fluid regime to match the dynamics of fluid leakage. In this context, an intervention to reduce plasma leakage to complement fluid therapy could offset the inherent drawbacks of a single modality of intervention and thwart the advent of life-threatening complications of DHF, particularly during epidemics that can overwhelm resource limitations.

Plasma leakage in DHF

Corticosteroids have been used to reduce plasma leakage, but there is inadequate evidence to support its use for this purpose. In my search for an interventional option, I have conceptualized the use of fresh frozen plasma (FFP) to reduce plasma leakage in DHF. Plasma leakage is the result of increased vascular permeability brought about by a cytokine storm without any vascular damage or inflammation. The quantum of cytokine production and, hence, the magnitude of plasma leakage is directly related to the viral load. Antibody-enhanced viral replication is a well recognized mechanism implicated in increasing the viral load. Immunoglobulins in FFP by Fc receptor blockade could compromise antibody enhanced viral replication by preventing the uptake by macrophages of dengue viruses.
complexed with non-neutralizing, cross-reactive, dengue-specific antibodies. Even though intravenous immunoglobulin has been used in dengue, it has been used late in the disease course on patients already in shock and there are no good randomized controlled trials (RCT) to date that have tested its efficacy when given early at the inception of plasma leakage.\textsuperscript{[10]} The basic Starling principle still holds true in explaining microvascular ultrafiltration based on the balance of the oncotic and hydrostatic pressures; but the glycocalyx, which is a gelatinous layer lining the inner surface of the vascular endothelium, is also implicated in controlling the fluid flow across the endothelium.\textsuperscript{[7,8,9]} Plasma proteins, particularly albumin, adsorb to the positively-charged residues in the glycocalyx and restrict ultrafiltration.\textsuperscript{[11,12,13,14,15]} Albumin in FFP, by adhering to the glycocalyx, could reduce the transfer of fluid across the vascular membrane. However, the beneficial effect of albumin in dengue, if any, could be evident only early in the disease course before shock, as in severe disease, albumin too leaks out of the vascular compartment. It is hypothesized therefore that when given early, FFP, by these two independent mechanisms, could reduce fluid fluxes across the vascular membrane in patients with DHF.

In a previous study designed to test the effect of FFP on thrombocytopenia in DHF, I made an incidental observation of a drop in the haematocrit (HCT) in the treatment arm of the randomized control trial (RCT), which was not evident in the control arm that received only isotonic saline, implying fluid retention in the face of increased vascular permeability in the group of patients who received FFP.\textsuperscript{[16]} J.S.D.K. Weeraman and I have carried out in-depth reviews into deaths related to dengue as well as random audits on the clinical management of DF and DHF from 1 September 2010 to 31 January 2011. These audits and reviews were done in state sector hospitals in the western, north western, central, north central, northern, Sabaragamuwa and the southern provinces in Sri Lanka, including the National Hospital of Sri Lanka, the Lady Ridgeway hospital for children, as well as a private hospital in Colombo. Out of a total of 34 patients on whom death reviews were done, 11 had received FFP. Out of a total of 45 patients on whom clinical audits were done, 12 had received FFP. We observed a drop in the haematocrit in 20 out of the total of 23 patients with DHF who had received FFP during the course of their management. Out of the 20 patients in whom the haematocrit dropped, four patients had overt gastrointestinal bleeding and all of them died. Seven out of the 20 patients in whom the HCT dropped were fluid overloaded, two of whom died. It is possible that bleeding as well as fluid overload could have contributed to the observed drop in the HCT among some (11 out of 20) of these audited patients. Whether FFP was a contributory factor to the drop in HCT by an independent mechanism, as hypothesized in this cohort, is conjectural. Nevertheless, all these incidental observations of a drop in the HCT in patients who had received FFP tend to support the hypothesized benefits of FFP used early in the critical phase in DHF. However, there are limitations in the interpretation of the drop in HCT among some of the patients in the audited cohort as blood loss and fluid overload could have been contributory factors other than the hypothesized reduction in plasma leakage. Before advocating the use of FFP as an intervention to reduce plasma leakage in DHF, it would be necessary to test this hypothesis by a RCT which I have designed but is awaiting ethical clearance for execution.
Discussion

An intervention to reduce the leakage of fluid out of the vascular compartment during the critical phase of plasma leakage in DHF could add a new dimension to the management of patients with DHF. I believe that a critically-timed dose of FFP in selected patients with DHF could effect a reduction in the morbidity and mortality due to DHF. It is based on my conceptualized hypothesis as well as personal experience in making incidental observations on DHF patients who had received FFP. This could be a major advance in the management of DHF as it utilizes an easily implementable and readily available intervention targeting an area of critical importance in the pathogenesis of a disease spreading globally, for which there is no specific therapeutic option available to date.

Until such time as we can complete our investigations, I can only advocate strict and diligent adherence to fluid therapy as detailed in the Sri Lankan national guidelines on the management of DF and DHF which have international applicability.

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