What treatments are effective for the management of shock in severe dengue?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:
http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What treatments are effective for the management of shock in severe dengue?*

The WHO Pocketbook of Hospital Care for Children recommends to give only isotonic solutions such as Ringer's lactate, Hartmann's solution or 5% glucose in Ringer's lactate. Patients in shock (Pulse pressure<20 mmHg) should be given20 ml/kg of isotonic fluid over one hour. If response occurs then the rate of fluid is reduced accordingly. If no response then a repeat bolus of isotonic fluid is recommended and consideration of 6% Dextran or 6% HES 10-15ml/kg over one hour is advised. Transfusions and are rarely necessary and should be only given with extreme care due to fluid overload. Platelet Transfusions should only be given for severe bleeding. Diuretics should be avoided in the case of fluid overload unless the shock has resolved. Steroids are not recommended. (Pocketbook section 6.10)

INTRODUCTION

Dengue hemorrhagic fever is a major cause of morbidity among children under 15 years of age. Worldwide 50-100 million cases of dengue fever occur annually of which hundreds of thousand are dengue hemorrhagic fever. Dengue is endemic in South East Asia, the Americas, western Pacific, the eastern Mediterranean and Africa. The more severe form of dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS) is characterized by severe vascular leakage and coagulopathy and progresses to death in 1 to 5 percent of cases. The pathophysiology underlying the systemic capillary permeability is poorly understood and no specific therapies are available. DSS develops when massive leakage of fluid from the intravascular space into the extravascular space occurs, usually between the third and fifth day of illness. The World Health Organization (WHO) has published guidelines for the diagnosis of DSS. They include presence of fever for 2-7 days, positive tourniquet test and/or spontaneous bleeding, thrombocytopenia (platelets =100,000 m3), evidence of plasma leakage (hematocrit =20% above expected mean, reduction of hematocrit by = 20% of the baseline value after fluid resuscitation, clinical presence of pleural effusion or ascites), and circulatory failure with pulse pressure =20 mmHg or hypotension (DHF III DSS). Profound shock many occur (DHF IV DSS) and is defined as undetectable pulse and blood pressure. Several therapies have been proposed in the management of DSS.

METHODOLOGY

The clinical search strategy employed was as follows: "dengue shock syndrome" using the clinical filters for both "therapy" and "specific", 9 articles were found; using the same filter but restricting the search to systematic reviews only no further articles were found.

All studies were RCT's; one was excluded because it was conducted on monkeys, a second trial was excluded because it was not blinded and had weak methodology.

No systematic reviews were found. The 7 articles included were type 1b and 2b.

RESULTS

The mainstay of treatment in DSS is intravenous fluids. No RCT's were found that compared IV fluids to placebo. It is widely accepted that IV fluids given at the appropriate time and in the appropriate volume are important in the treatment of DHF and DSS. A study comparing IV fluid to placebo would be considered unethical.

3 studies have been conducted comparing crystalloids to colloids in the treatment of DSS. The first study in 1999 of 50 Vietnamese children ages 5-15 compared four intravenous fluid regimens (Ringer's lactate, normal saline, 3% gelatin and dextran 70) and showed no difference in the duration of shock (p=.36) or the number of episodes of shock (p=.46) between fluid groups. They also showed no difference in the requirement for more crystalloid infusions (p=.16) or colloid infusion (p=.70) following the initial resuscitation between groups. All children recovered in each group. This study was likely underpowered to find a difference between the four intravenous fluid regimens. [1]

The second study in 2001 of 230 Vietnamese children ages 1-15 years also compared four intravenous fluid regimens (Ringer's lactate, normal saline, 3% gelatin and dextran 70). They used the WHO definition of shock in DHF III (DSS) as a pulse pressure =20 mmHg and noted within this group there was a more "severe" group of patients who presented with a pulse pressure of =10 mmHg. Their study also included 8 patients with DHF IV (DSS) who presented with undetectable pulse and blood pressure. They found a small but significant difference in the median pulse pressure recovery times between the four groups favouring colloids (p=.03) but after Bonferroni adjustment the only significant difference was between dextran and normal

saline (p=.036) However, fewer patients with an initial pulse pressure =10 mmHg were in the dextran group compared to other fluid groups after randomization which may have confounded this result. When colloids were compared to crystalloids in children with a pulse pressure =10-20 mmHg no difference was found (p=.107). 51 of 230 presented with pulse pressure =10 mmHg. Within this smaller group there were significant differences in the median pulse pressure recovery time favouring colloids versus crystalloids as the initial resuscitation fluid (p=.01) and in the proportion of patients whose recovery took >1 hour (p=.037). Of the 8 patients with DHF IV 3 received colloids and 5 received crystalloids. They also showed a trend towards improved outcome with early colloids with a shorter period of time to recovery of pulse pressure (30 min vs. 60 min). Overall, they found no difference between fluid groups in occurrence (p=.992) or timing of subsequent episodes of shock (p=.68). They also found no difference in the total volume of intravenous fluids received until full recovery (p=.95) or in the number of patients requiring furosemide for the treatment of fluid overload (p=.328). They had no deaths in the study group. The authors concluded that they were unable to demonstrate a clear benefit of any of the four fluids in the 222 children with DHF grade III, however their subgroup analysis suggested that more severely ill patients may benefit from early colloid administration. They felt a larger study powered to detect these potential differences should be undertaken.[2]

The third study in 2005 of 512 Vietnamese children ages 2-15 years compared 3 intravenous fluid regimens (Ringer's lactate, dextran 70 and 6% hydroxyethyl starch). Based on the authors' previous work they stratified their study into 2 groups, group 1 moderate shock (pulse pressure of >10 and =20 mmHg) and group 2 severe shock (pulse pressure = 10 mmHg). Patients in group 1 (n=383) were randomized to receive Ringer's lactate, dextran or starch and group 2 (n=129) dextran or starch. The primary outcome was need for rescue colloid any time after infusion of the study fluid. In the patients with moderately severe shock (group 1) there was no difference in the number of patients who received rescue colloid in any of the 3 fluid groups (RR 1.08,CI 0.78-1.47). In patients with severe shock there was no difference in the number of patients who received rescue colloid in either of the 2 fluid groups (RR 1.13, CI 0.74-1.74). Thus, there was no difference in either severity group in the requirement for colloid subsequent to the initial episode of shock (p=.38), in the volumes of rescue colloid (p=.16), total parenteral fluid administered (p=.17), or in the number of days in the hospital (p=.81). The authors showed no benefit to treatment with colloids over Ringer's lactate (crystalloid) in the treatment of moderate shock (pulse pressure >10 to = 20 mmHg). They also showed no clear benefit to either dextran or starch in the group with severe shock (pulse pressure = 10 mmHg). There was one death in group 2. Although there is no clear evidence to support the use of colloids initially in children with "severe" shock, the authors felt it was unethical to compare crystalloids to colloids in this group because the use of colloids is largely accepted as beneficial. Further studies are needed in this high risk group. [3]

2 randomized controlled trials have compared steroids to placebo in children with DSS. The first study in 1981 compared a single dose of 50mg/kg of hydrocortisone to placebo in 97 Indonesian children less than 15 years old with DSS. All children received standard treatment with IV fluids. The primary outcome of the study was change in the WHO scoring system for the effectiveness of treatment. There was no difference found between groups (p>.05). The secondary outcome was mortality and again there was no difference between groups (p>.05). The negative outcome of this study must be interpreted with caution as no power calculation was reported in the study. [4] The second study in 1993 compared a single dose of 30 mg/kg of methylprednisolone to placebo in 63 Thai children with DSS. All children received standard treatment with IV fluids. The primary outcome of the study was all cause mortality. 4 of 32 patients in the methyprednisolone group (12.5%) and 4 of 31 patients in the placebo group (12.9%) died. There was no significant difference in the case fatality rate (p=.63, 95% CI -17% to +16%). The authors had assumed a 90% fatality rate for their power calculation. The study had much less power than planned and the negative result must be interpreted with caution. [5]

1 randomized controlled trial compared the ability of carbazochrome sodium sulfonate (AC-17) to prevent capillary permeability in DHF/DSS versus placebo. 95 Thai children less than 14 years of age with a presumptive diagnosis of DHF/DSS were included. The primary outcome was the prevention of capillary leakage as evidenced by the presence of pleural effusion. No difference was found in the rate of pleural effusion seen between the AC-17 group (33.3%) and the placebo group (30%, p=0.89). The secondary outcome was prevention of the development of shock. Shock developed in 4 (8.9%) patients during the course of treatment in the AC-17 group and 3 (6%) in the placebo group (p=0.44, 95% CI -7.7% to +13.5%). The authors calculated that 220 patients would be required to reduce the rate of pleural effusion from 30% to 15%. Thus, the negative results of this study must be viewed with caution as the sample size was inadequate.[6]

1 randomized controlled trial compared Nasal Continuous Positive Airway Pressure (NCPAP) to oxygen delivered by facemask in DSS with acute respiratory failure (defined as cyanosis, tachypnea or severe chest retraction and nasal flaring while on 40 per cent oxygen by nasal canula). 37 Vietnamese children under 15 years of age were studied. The primary outcome was patient stabilization (defined as paO2 > 80 mmHg) after 30 minutes. There was no significant difference in failure to stabilize the patient between the 2 groups following the first 30 minutes of treatment. There was a significantly higher rate of ongoing unresponsiveness to treatment in the oxygen mask group compared to the NCPAP group (13/19 vs. 4/18, p < 0.01). Of the 13 patients who failed treatment with O2 by facemask all received NCPAP and improved. Of the 4 patients who failed treatment with NCPAP all were intubated and ventilated and all 4 died. NCPAP effectively decreased hypoxemia and reduced the number of children requiring intubation and ventilation in children with DSS and acute respiratory failure. Limitations of the study were small numbers which resulted in partly incomparable groups in terms of sex, weight and total volume of fluid infused before admission. However, there was no difference in the number of patients with pleural effusions in each group. [7]

SUMMARY

The only known effective treatment in DSS is timely, aggressive fluid resuscitation. For children with DHF III there is no evidence that colloids are superior to crystalloids for initial resuscitation (Grade A evidence). No study has directly investigated whether colloids offer an advantage to crystalloids in patients with severe DHF III (pulse pressure <10 mmHg) or DHF IV. Current clinical practice is to use colloids as an initial resuscitation fluid in these patients (Grade C evidence). With appropriate use of fluid resuscitation in DSS mortality rates have been shown to be <0.2%. Steroids have not been proven to beneficial in DSS but existing studies may have been underpowered to detect a treatment benefit (Grade B evidence). AC-17 has not been shown to be beneficial in DSS but the study

was underpowered to detect a potential treatment benefit (Grade B evidence). NCPAP is an effective treatment in acute respiratory failure associated with DSS (Grade B evidence).

CLINICAL BOTTOM LINE

Appropriate, aggressive fluid resuscitation in patients with DSS significantly reduces mortality. NCPAP is effective in children with DSS complicated by acute respiratory failure.

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