Research Article

Fluid Management in Patients with Dengue Hemorrhagic Fever

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ABSTRACT

Introduction and background

Iatrogenic fluid overload in Dengue Haemorrhagic Fever (DHF) is well recognized. To address this, restriction of total fluid volume in the critical phase (TFV) to maintenance plus 5% of the body weight (M+5%) was adopted in Sri Lanka in 2010. The purpose of this study was to assess the TFV and how it relates to fluid overload, bleeding and liver dysfunction. Further we assessed how the disease severity at presentation (DSP) i.e. the presence or the absence of Dengue Shock (DSS), affects TFV and the above complications.

Method

A retrospective cohort study on 401 DHF patients admitted to Lady Ridgeway Hospital from March to August 2011. Associations of TFV and DSP with each other and with the above complications were analysed using unconditional logistic regression and Student's t-test as appropriate.

Results

In 2/3rd of the sample, TFV>M+5%. 34.4% developed fluid overload, 16.7% developed bleeding and 63.1% developed liver dysfunction. Fluid overload showed a very significant association with the TFV (OR= 5.51, CI 3.17-9.57) yet was not associated with the DSP. Bleeding was associated with both TFV (OR=2.12, CI 1.12-4.02) and DSP (OR= 2.81, CI 1.56-5.08). Liver dysfunction was associated with DSP (p=0.03) yet not with TFV. Association of TFV with DSP was not significant (p= 0.28)

Conclusions

Use of excess fluid in the critical phase is significantly associated with fluid overload and bleeding. Thus the importance of following M+5% fluid guidelines is emphasized to achieve better outcomes.

Dengue shock at presentation associates with increased risk of bleeding and liver dysfunction.

The demonstrated association of excess fluid with bleeding has not been described in the previous literature.

Keywords: dengue haemorrhagic fever, dengue shock, fluid management, complications

Introduction

Dengue hemorrhagic fever (DHF) is a major public health problem in Sri Lanka and it is one of the leading causes for hospital admissions.

Management of DHF is challenging and primarily depends on very close monitoring and judicious fluid management. Delicate fluid management in the critical phase of the illness is of paramount importance for better outcomes.[1, 2]

Studies done in Thailand show that Maintenance + 5% Fluid regime during the critical phase has been able to reduce the case fatality rates of DHF significantly[3]. Guidelines based on this regime were adopted in Sri Lanka and were incorporated into the National Guidelines on the management of DHF in December 2010. However, there are no data available on the fluid management after the adoption of new guidelines in Sri Lanka.

In this study we assessed the fluid management of patients with DHF during the dengue peak of March 2011 to August 2011.

General objectives

To assess the fluid management in the critical phase of dengue haemorrhagic fever

Specific objectives

To assess the

1. Total volume of fluid used during the critical phase
2. The type of fluids used (crystalloid, colloid)
3. The frequency of blood and blood products use
4. Disease severity at presentation(DSP) i.e. Dengue shock (DHF grade 111or 1v) or no shock
5. The occurrence of complications (fluid over load, liver dysfunction ,bleeding manifestations) and relationships to
    a) total volume of fluid used
    b) Disease severity at presentation

Method

This retrospective cohort study was carried out at the Lady Ridgeway Hospital for Children, Colombo, Sri Lanka from March to August 2011

DHF patients admitted to all the medical wards during the specified period were included in the study except those aged 12 months or less.

DHF was diagnosed according to the WHO case definition criteria [4,5]viz...High fever, Haemorrhagic manifestations, Thrombocytopaenia of <100000/mm^3, evidence of leaky capillaries (rise of haematocrit>20%[5, 6, 7] / or radiological evidence)

Data were collected from Bed Head Tickets using a purpose designed data collection sheet, by the principal investigator and trained assistants. Age, body weight, Disease severity at presentation (shock, non-shock), total volume of fluids used in the critical phase and the type of fluid, fluid boluses (colloids and crystalloid), use of blood and blood products were recorded.

Occurrence of below mentioned complications were recorded.

a) fluid overload

b) liver dysfunction

c) bleeding manifestation

Record of tachypnoea/ basal crepts / use of frusemide were taken as indicators of fluid overload.

Malena, haematemesis, mucosal bleeding were taken as evidence of bleeding manifestations.

Presence of elevated liver transaminases (SGOT) three times more than the upper limit was taken as evidence for liver dysfunction.[8] (Lab normal reference value for SGOT- 9-48 u/l)

Results were analyzed with the statistical package SPSS.

Initially descriptive statistics (frequency/ percentages) of volume of fluid used, use of fluid boluses and use of blood products were assessed.

Association of liver dysfunction with the disease severity at presentation and use of fluid more than M+5% was analyzed using student's T test.

Association of bleeding manifestations and fluid over load with the use of fluid more than M+5%, circulatory status on admission and age were analyzed using unconditional logistic regression.

Results and Analysis

A total of 401 patients were included in the study. Age ranged from 1 to 12 years.

1. **Fluid volumes in the critical phase;**

M = Maintenance fluid calculated by holyday Segar formula

Table 1 - No of patients in each fluid category

Fluid category	No. of patients	Percentage %
M to M+2.5%	53	13.2
M+2.5% to M+5%	84	20.9
M+5% to M+7.5%	88	21.9
M+7.5% to M+10%	72	18.0
> M+10%	104	25.9

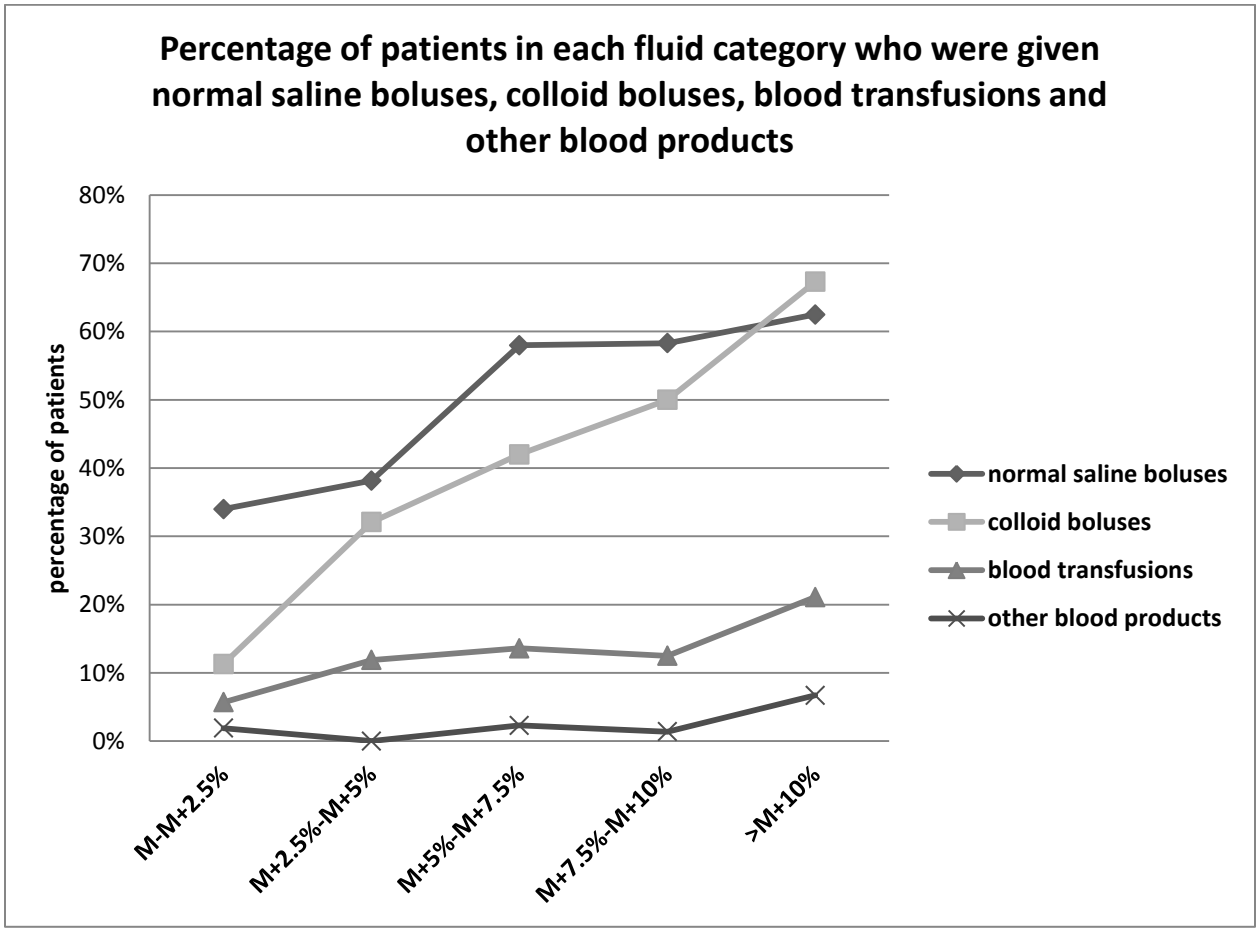
Only one third (34.1%) of the total number of patients received fluid within the recommended fluid quota (i.e. <M+5%). The fact that one quarter of the total number (25.9%) received even more than M+10% is noted as well. The distribution of volumes of fluid received across the population was not a normal distribution and it was rather skewed towards higher fluid quotas.

2. **Fluid types;**

While the maintenance fluid had been crystalloid (normal saline), boluses of crystalloid and colloids plus blood and blood products were used as when needed.

Crystalloid boluses were the most frequently used except in the >M+10% category. (When colloid boluses had been used more frequently)
Use of all types of fluid rises when moving up on the fluid category yet the most marked and the steepest rise is in colloid followed by crystalloid boluses.
Less number of patients were given blood or blood products. Blood transfusions were given to 14.2% of the total subjects while 2.7% were given blood products.

Graph 01



3. **Disease severity at presentation**

Out of the total patients, 74 (18.4%), were in shock state on admission. Table 3 describes how this relates to fluid category. In the shock group, higher percentage (71.6%) had fluid >M+5%. When compared with non shock group (64.5%). Yet this difference was not statistically significant. (P=0.28)

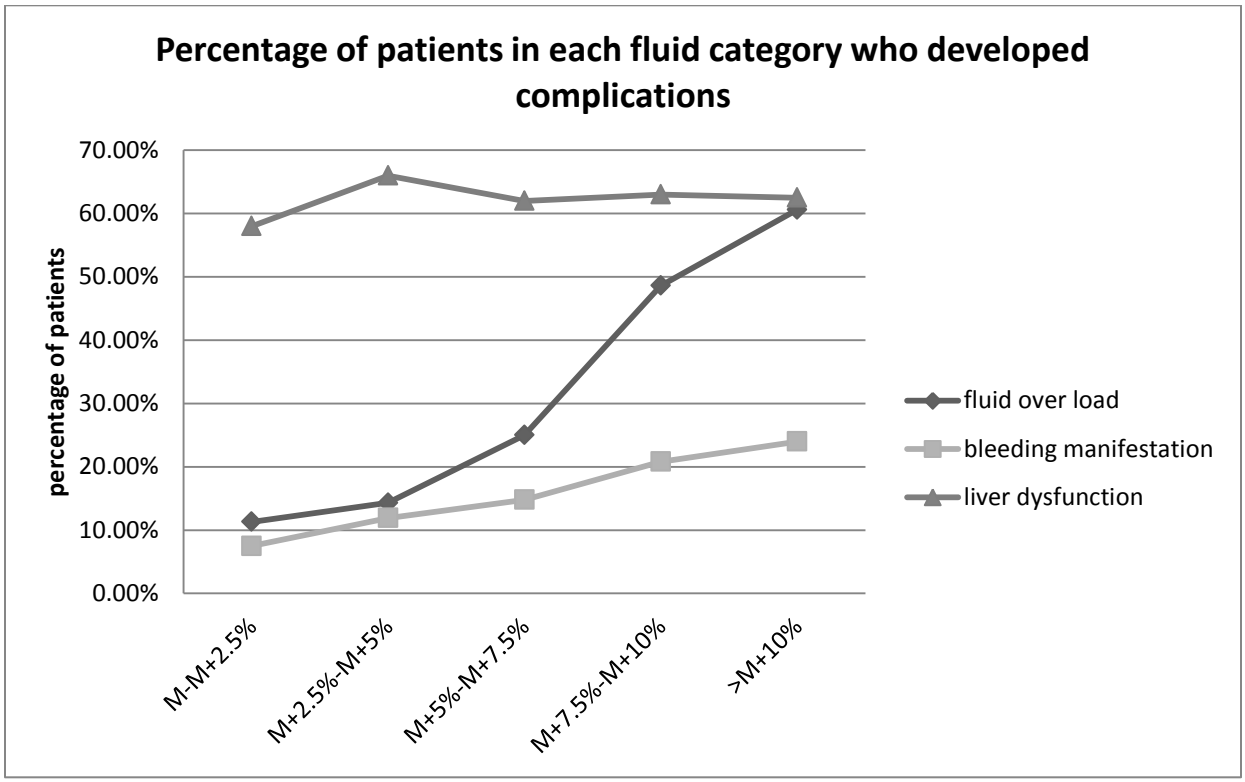
Table 2: Disease severity at presentation in each fluid category.

Fluid category	Shock on admission (DSS+)	No shock on admission (DSS-)
M to M+2.5%	5 (9.4%)	48 (90.6%)
M+2.5% to M+5%	16 (19%)	68 (82.9%)
M+5% to M+7.5%	22 (25%)	66 (75%)
M+7.5% to M+10%	11 (15.2%)	61 (84.7%)
> M+10%g	20 (19.2. %)	84(80.7%)
total	74	327

4. Complications

Out of 401 subjects, 138(34.4%) developed fluid overload, 67(16.7%) developed bleeding manifestations and 253(63.1%) developed Liver dysfunction.

Graph 2



Liver dysfunction remains around 60% across all fluid categories.Fluid overload and bleeding manifestations increase with the fluid category.

Fluid overload which is 11.3% in the first fluid category increases to a very high 60.6% in the fifth fluid category. The increase is exponential specially so when the fluids increase beyond M+5%.

Bleeding manifestations increase from 7.5% in the first fluid category to 24.0% in the fifth fluid category. The increase is more or less linear.

Complications vs Disease severity at presentation (DSS -/ DSS +)

Out of the 74 patients who presented with shock, 32(43.2%) developed fluid overload, bleeding manifestations were seen in 23 (31.1%), while liver dysfunction was seen in 50(67.5%)

Out of the patients who did not have shock on admission (n=327), Fluid overload was seen in 106(32.4%), Bleeding was seen in 44(13.4%) and liver dysfunction was seen in 203(62%).

5. **Analysis of associations**

Complications were further analyzed to assess the association with the following variables:

I. Use of fluid more than M+5%,
II. Disease severity at presentation
III. Age

Unconditional logistic regression was used to assess the association of bleeding manifestations and fluid overload with the above variables.

Age was not significantly associated with any complication.

Fluid overload was significantly associated with the use of fluid more thanM+5% (OR= 5.51, CI= 3.17-9.57) yet not with disease severity at presentation

Bleeding manifestations showed significant association with the use of fluid more than M+5% (OR=2.12 , CI= 1.12-4.02) and dengue shock state on admission.(OR=2.81, CI=1.56-5.08)

Liver dysfunction and association with the above variables were assessed using the student's t-test. There was significant association between liver dysfunction and DSP(p=0.03). Yet there was no significant association with the use of fluid more than M+5%. (See table 07)

Discussion

Capillary leakage and Fluid overload

The dengue virus is not known to infect endothelial cells. The fluid leakage through the endothelium in the critical phase is possibly caused by cytokine mediated increase in vascular permeability and a transient disruption in the surface glycocalyx.[9]

Target of intravenous fluid therapy is to compensate for this fluid leak. Yet this can easily be overdone. Once the normal endothelial permeability regained and leaked fluid starts returning, a fluid overload can develop. This could cause pleural effusions, ascites, pulmonary oedema (resulting in hypoxaemia). In some cases could be so severe even to account for fatalities.

In the light of this problem, concept of fluid sealing in the critical phase (maintenance +5% of the body weight) was devised at the turn of the century.

It is important to recognize that similar concepts were developing in other fields of medicine as well in contemporary times. The concept of 'fluid creep' in burn patients caused by overenthusiastic fluid resuscitation was recognized in 1990's[10,11]. Dynamic control of fluid resuscitation to have a urine output of 0.5-1 ml/kg/hour led to better outcomes. The concept of 'hypotensive resuscitation' in trauma patients was developing in the same era[12]. Better outcomes were achieved by controlled resuscitation maintaining systolic blood pressure between 90-100 mmhg(adult values).

In the current study 2/3rd (65.8%) of the patients received fluid volumes (TFV) beyond the recommendations. Further, that there is an exponential increase of the fluid overload when the TFV is more than M+5%. The association of fluid overload when the total volume of fluid exceeds the calculation , was noted in the study done by Duangporn Asawarachun as well[13.]

Bleeding

Bleeding in DHF is thought to be caused by aberrant immune responses against endothelial cells, platelets, monocytes and hepatocytes which trigger a consumption coagulopathy [14]. Bleeding has been found to correlate with disease severity.[14]

In the current study we have found that the bleeding risk correlate with the Disease severity at presentation whereby patients who presents in shock status are nearly three times more likely to develop bleeding when compared to normal circulatory status at presentation (odds ratio= 2.81 95% CI= 1.56- 5.08).

Other fact we have shown is that the patients who receive more fluid are more likely to bleed. Those who receive fluid > M+5% are nearly two times more likely to bleed than who receive fluid < M+5 %.(OR= 2.12, 95% CI= 1.12- 4.02).

There are two possible explanations for the association of bleeding with high fluid. Firstly, as the bleeding in dengue is thought to be due to a consumption coagulopathy, the overuse of fluid may be exerting a dilutional effect on already deficient coagulation factors. Secondly, increased fluids and resultant increase in capillary hydrostatic pressure may be exerting a physical stress and causing a transient destruction of the surface glycocalyx resulting in endothelial dysfunction.[14]

Liver dysfunction

Three factors are thought to be contributing to hepatic dysfunction in dengue. Firstly the dengue virus itself has been demonstrated to be actively replicating in hepatocytes and causing cytopathic effect. Further, hypoxemia due to shock and host responses to infection are thought to be causative.[14]

Our study shows that the hepatic dysfunction is associated with shock states at presentation with the P value of 0.03. This finding supports the hypothesis that hypoxaemia due to shock may be playing a role. The association of hepatic dysfunction with Dengue shock syndrome was noted also in the study done by W.Petdachai .[14]

Limitations

1. There are two possibilities for a patient to receive higher fluid volumes. Firstly there could have been a true clinical need caused by excessive fluid leakage. Secondly it could be overzealous fluid usage. If we had analyzed urine output we could have commented on this fact.

2. Dengue deaths during this period were not analyzed as there was difficulty in retrieving the data.

Conclusions

Use of excess fluid in the critical phase is significantly associated with fluid overload and bleeding. Thus the importance of following M+5% fluid guidelines is emphasized to achieve better outcomes.

Shock status on presentation leads to three folds increase in the risk of bleeding. It is significantly associated with liver dysfunction as well. Thus in patients presenting with circulatory shock, increased risks of bleeding and liver dysfunction are to be anticipated.

The demonstrated association of use of excess fluid with bleeding as a complication is a new finding not hitherto described in literature.

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