

TABLE I RISK OF HYPONATREMIA WITH HYPOTONIC VS ISOTONIC MAINTENANCE FLUID

Time	Fluid type*	Hyponatremia (%)	Risk difference (95% CI)	NNH(95% CI)	P value
At 24 h	IF	7 (23.3%)	30% (6.6% - 53.4%)	4 (1.9-15.2)	0.03
	HF	16 (53.3%)			
At 48 h	IF	4 (13.3%)	30% (8.5% - 51.5%)	4 (1.9-11.8)	0.02
	HF	13 (43.3%)			
Overall	IF	10 (33.3%)	36.7% (13.1% - 60.2%)	3 (1.7-7.6)	0.01
	HF	21 (70%)			

*IF, Isotonic fluid; HF, Hypotonic fluid; N =30 for each fluid type; NNH: number-needed-to-harm.

potassium were to be used in both groups, the concentration of potassium would have been 60% higher in the isotonic fluids group (33.3 meq/L as against 20 meq/L). Moreover, this would have also increased the tonicity of the fluid by approximately 7.5%. For maintaining infusion concentration at 20 meq/L, potassium supplementation needed to be reduced.

We agree that urine osmolality should also have been measured to estimate free water clearance and could have explained hyponatremia despite using isotonic fluids.

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REFERENCES

1. Shamim A, Afzal K, Manzir AS. Safety and efficacy of isotonic (0.9%) vs. hypotonic (0.18%) saline as maintenance intravenous fluids in children: A randomized controlled trial. *Indian Pediatr.* 2014;51:969-74.
2. Montanana PA, Modesto AV, Ocon AP, Lopez PO, Lopez PJJ, Toledo PJD. The use of isotonic fluid as maintenance therapy prevents iatrogenic hyponatremia in pediatrics: a randomized, controlled open study. *Pediatr Crit Care Med.* 2008;9: 589-97.
3. Kannan L, Lodha R, Vivekanandhan S, Bagga A, Kabra SK, Kabra M. Intravenous fluid regimen and hyponatraemia among children: A randomized controlled trial. *Pediatr Nephrol.* 2010;25:2303-9.

Atypical Features of Severe Dengue: Probable Pathogenesis

Severe dengue typically consists of hypovolemic shock (dengue shock syndrome) and bleeding (dengue hemorrhagic fever) [1,2]. Two recent papers in *Indian Pediatrics* highlight “atypical” features of severe dengue, mainly as organ failure – liver, heart, lungs, kidneys, brain – in any combinations [1,2]. These are increasingly being recognized in recent years [1-3]. We suspect that these might be – at least partly – iatrogenic, associated with unwarranted platelet transfusions, a popular practice in recent years [4, 5].

Thrombocytopenia is characteristic of dengue fever and severe dengue. Hemophagocytosis and bone marrow suppression are the frequently described causes for thrombocytopenia [4]. We propose another pathway for platelet depletion, which has an important bearing on possible adverse effects of platelet transfusions [4].

We believe that platelets get sequestered on small vessel endothelial cells in dengue, similar to what happens in microangiopathy of thrombotic thrombocytopenic purpura (TTP) [4]. The adhesion ligand is von Willebrand factor (vWF). Increased vWF activation or decreased cleavage of vWF by protease ADAMTS 13 will result in increased adhesion and platelet microthrombi [4]. In severe dengue, the balance between vWF and ADAMTS 13 is deranged [4]. Deficiency of ADAMTS 13 will result in extremely adhesive, ultra-large vWF multimers, resulting in platelet microthrombi [4].

Microvascular plasma leakage causes hypovolemia in which low platelet counts seem not to be involved, at least directly. Small vessel bleeds do not get plugged by platelets as their numbers are grossly depleted, thus leading to uncontrolled bleeding at various sites. But, what is the pathogenesis of organ failure? We propose that platelet microthrombi obstruct perfusion resulting in organ hypoxemia and failure [4]. We suspect that multi-organ failure may be partly due to platelet transfusions

given in an attempt to correct thrombocytopenia as the added platelets may increase platelet microthrombi and further reduce organ perfusion. Standard treatment protocols for severe dengue do not recommend platelet transfusion as it does not seem to help in any manner [4, 5].

The authors describing atypical manifestations have not clarified if patients were given platelet transfusions [1-3]. When platelet transfusion is felt to be life-saving in the face of serious bleeding, ADAMTS 13 ought to be given prior to platelet transfusion, in order to prevent platelet adhesion aggravating the problem. Fresh frozen plasma and cryosupernatant are rich in ADAMTS 13 [4]. Fresh whole blood transfusion, as recommended by WHO will also supply ADAMTS 13 [4].

When severe dengue is diagnosed, especially with suspicion of impending organ failure, infusion of fresh frozen plasma is a relatively easy intervention for reducing platelet adhesion. More heroic measure would be plasma exchange for diluting out excess vWF (4). Recently, recombinant ADAMTS 13 has become available, and is another intervention that needs to be studied [4].

We strongly recommend the avoidance of platelet transfusions. Investigations to evaluate the benefits (particularly mortality reduction) of fresh frozen plasma,

plasma exchange and recombinant ADAMTS 13 in patients with severe dengue are urgently required. Those who see large numbers of cases of severe dengue are urged to investigate the questions raised above. If proven correct, many lives may be saved by strict adherence to recommended management of dengue.

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REFERENCES

1. Pawaria A, Mishra D, Juneja M, Meena J. Atypical manifestations of dengue fever. *Indian Pediatr.* 2014;51:495-6.
2. Pothapragadia S. Atypical manifestations of dengue fever. *Indian Pediatr.* 2014;51: 937-8.
3. Verma R, Sharma P, Garg RK, Atam V, Singh MK, Mehrotra HS. Neurological complications of dengue fever: Experience from a tertiary center of north India. *Ann Indian Acad Neurol.* 2011;14:272-8.
4. Eapen CE, Elias E, Goel A, John TJ. Hypothesis of mechanism of thrombocytopenia in severe dengue, providing clues to better therapy to save lives. *Current Science.* 2015 (in press).
5. Makroo RN, Raina V, Kumar P, Kanth RK. Role of platelet transfusion in the management of dengue patients in a tertiary care hospital. *Asian J Transfus Sci.* 2007;1: 4-7.