

Furosemide Infusion in Children with Dengue Fever and Hypoxemia

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Objectives: To study the role of furosemide infusion in the management of Acute respiratory distress syndrome (ARDS) associated with dengue fever.

Methods: Children between the ages of 1 month to 18 years, who fulfilled the WHO clinical criteria for dengue infection and American European Consensus Criteria criteria for ARDS with Dengue IgM positivity, were evaluated. Patients were studied as group D (receiving diuretic therapy alone) and group B (both ventilation and diuretics), and compared to a historical control group V (ventilation alone). Furosemide infusion was

administered at 0.05-0.1 mg/kg/hour for 48 hours, maintaining a urine output of 2-4 mL/kg/hour.

Results: There was a significant difference in survival in the three groups. Significant difference was noted between pre- and post-intervention arterial blood gases with respect to PCO_2 ($P=0.02$), pO_2 ($P=0.003$), PaO_2/FaO_2 ratio ($P<0.001$) and alveolar-arteriolar oxygen gradient ($P=0.002$).

Conclusion: Diuretic infusion improves outcome in dengue with ARDS.

Keywords: ARDS, Dengue, Diuretics, Outcome.

Dengue hemorrhagic fever (DHF) and Dengue Shock Syndrome (DSS) constitute important causes of death, with protean clinical manifestations, in those infected with the dengue virus. The mortality rate with severe forms of dengue infection may approach 47% [1]. Only one of three children with associated Acute respiratory distress syndrome (ARDS) survives [2]. ARDS complicating dengue fever is reported with an estimated frequency of 2.4% [3,4].

The World Health Organization (WHO) guidelines [5] offer a useful approach to immediate fluid resuscitation in various stages of the disease. Kabra, *et al.* [6] and Soni, *et al.* [7] have described difficulties in fluid management in children in the Indian context. Published data suggest maintaining a negative fluid balance for improved outcomes in ARDS [8]. Studies have demonstrated lower extra-vascular lung water, lesser mechanical ventilation and better survival with fluid restriction in comparison to standard fluid protocols [9]. Data to support the role of diuretics in pediatric ARDS are scarce [10]. Recently, Ranjit, *et al.* [11] described successful management of complicated dengue infection with judicious fluid removal. The objective of present study was to evaluate the role of diuretic infusion in improving respiratory parameters and mortality in children with dengue fever complicated by ARDS.

METHODS

This prospective study was conducted in Indira Gandhi

Institute of Child Health, a tertiary care referral centre with a 25-bedded pediatric intensive care unit (PICU) and 20-bedded dengue ward. Ethical clearance from the Institution's ethical committee was obtained to conduct this study. Participants included children between 1 month to 18 years of age diagnosed with dengue fever as per the WHO clinical definition. ARDS was defined as per the American European Consensus Criteria [12]. Evidence of left atrial hypertension was assessed clinically and by echocardiography. Disease severity of dengue fever was graded as per the WHO guidelines and by Pediatric Risk of Mortality (PRISM) III scores.

Patients included between September 2010 and December 2011 were considered group D in whom diuretic therapy was introduced as a modality of treatment. Those who subsequently required ventilation were considered group B. Children who were diagnosed with dengue fever with ARDS prior to the introduction of diuretic therapy (between December 2009 and August 2010) were considered group V (who were all ventilated as the only modality of treatment). Furosemide infusion was used at a dose of 0.05-0.1 mg/kg/hour and was titrated to maintain a urine output of 2-4 mL/kg/hour. Arterial blood gases before and after 48 hours of starting diuretic therapy were compared.

The chi-squared test was used to compare the difference between proportions. Student's *t*-test was conducted to compare means. 95% confidence intervals of data were calculated from means. The Mann-Whitney

TABLE I BASELINE CHARACTERISTICS OF STUDY SUBJECTS (N=110); No.(%)

Age of study subjects	Group D (Diuretics only)		Group V (Ventilation only)		Group B (Diuretics with ventilation)	
	Survivors	Non-survivors	Survivors	Non-survivors	Survivors	Non-survivors
< 1 year	3 (6.6)	0 (0)	1 (33.3)	3 (7.6)	1 (50)	1 (5)
1 - 5 years	12 (26)	0 (0)	2 (66.7)	10 (25.6)	1 (50)	5 (25)
5 - 10 years	16 (34.8)	0 (0)	0 (0)	12 (30.7)	0 (0)	6 (30)
10 -18 years	15 (32.6)	0 (0)	0 (0)	14 (35.9)	0 (0)	8 (40)
Total (survival rate)	46 (100)	0 (0)	3 (7.2)	39 (92.8)	2 (9)	20 (91)

U nonparametric test was used to determine differences between medians of groups. *P* value of less than 0.05 was taken as significant.

RESULTS

Of the 1525 children admitted with dengue fever, 110 developed ARDS, accounting for an incidence of 7.2%. Group D, V and B consisted of 46, 42 and 22 children respectively. Three children were withdrawn from the study and diuretic infusion was stopped in view of systemic hypotension requiring inotropic support. All 110 children were dengue IgM positive. The mean (SD) time of onset of ARDS from the first symptom was 7.5 (2.5) days.

Table I shows the baseline characteristics and outcome. There was no significant difference in mortality with respect to age ($P=0.09$) or gender ($P=0.5$). The survival rates were 100%, 7.2% and 9% in group D, V and B, respectively ($P<0.001$). There was no statistical difference in the grades of dengue fever or PRISM III score between survivors and non-survivors in group V ($P = 0.4$). In group B, PRISM III score of survivors was 12.5 and 16.5 for non-survivors ($P = 0.05$). Groups D and V were comparable by both WHO grading of DHF and mean PRISM III score.

Table II compares the arterial blood gases of children in Group D before and 48 hours after initiating diuretic therapy. There was a significant difference in pCO₂, pO₂, PF ratio and A-a gradient pre- and post-intervention.

DISCUSSION

The present study demonstrated the efficacy of furosemide infusion in ARDS with dengue infection. There was also a significant difference in survival between those children who received furosemide infusion alone and those who failed diuretic therapy and required mechanical ventilation. A significant increase in all these parameters is noted following furosemide infusion, thus demonstrating an improvement in

oxygenation.

Our results are similar to the report by Ranjit, *et al.* [11] who demonstrated the efficacy of fluid removal using diuretics or dialysis in children with dengue fever. The efficacy of furosemide infusion with respect to changes in the arterial blood gas demonstrates its role in respiratory function.

Many patients with dengue fever who fulfill the criteria for ARDS may actually be in a state of fluid overload. It is known that in the recovery phase of dengue fever, there is reabsorption of fluid from the extra vascular compartment. In these patients, diuretics should be tried, which could improve oxygenation and avoid the need for mechanical ventilation.

This study was limited due to the insufficient data available regarding the total fluid intake and output of the patients. Also, in comparing with historical controls, there were associated confounding factors such as different caregivers and a different support structure. The potassium and magnesium values were not measured before and after intervention. A high mortality rate in the ventilated group of patients could be due to late referrals and high incidence of nosocomial infections. ARDS is an important complication of dengue fever, which needs to be recognized and treated early. Furosemide infusion could improve survival in

TABLE II PRE-INTERVENTION AND POST-INTERVENTION ARTERIAL BLOOD GAS IN GROUP D (ONLY DIURETIC THERAPY)

Values	Pre-intervention Mean (SD)	Post-intervention Mean (SD)	<i>P</i> value
pH	7.43 (0.07)	7.40 (0.06)	0.18
PCO ₂	25.92 (8.85)	31.41 (6.92)	0.02
PO ₂	73.84 (27.2)	102.43 (38.5)	0.003
PaO ₂ /FiO ₂	167.51(50.3)	332.29 (153.7)	<0.001
A-a gradient	182.47 (75.8)	71.99 (127.9)	0.002

WHAT THIS STUDY ADDS?

- Furosemide infusion improves survival in the management of Dengue fever with ARDS, with significant improvement in oxygenation.

developing countries where access to mechanical ventilation is limited and its outcome is poor.

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