Randomized Comparison of Oxygen Mask Treatment vs. Nasal Continuous Positive Airway Pressure in Dengue Shock Syndrome with Acute Respiratory Failure

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Summary
Dengue hemorrhagic fever (DHF) is caused by dengue virus. Patients with DHF grade 3–4, termed Dengue Shock Syndrome (DSS), may develop acute respiratory failure after initial fluid resuscitation. Previously, these patients were treated with oxygen on a nasal cannula, or if necessary with tracheal intubation and mechanical ventilation. In the present prospective randomized study, we compared the effectiveness of oxygen treatment administered by a face mask vs. nasal continuous positive airway pressure (NCPAP). Morbidity, mortality, and supportive treatment was evaluated. Thirty-seven patients with DSS complicated by respiratory failure were enrolled. On admission and after 30 min of treatment, clinical and paraclinical data were obtained. Chest X-ray revealed pleural effusion in 92 per cent and showed interstitial oedema in 33 per cent. After 30 min of treatment the respiratory rate decreased significantly in the NCPAP group ($p < 0.05$), while $\text{SaO}$_2 and $\text{PaO}$_2 increased in both groups ($p < 0.01$). However, subsequently a significant difference of unresponsiveness to treatment between the oxygen mask group and the NCPAP group (13/19 vs. 4/18, $p < 0.01$) was noted. Complications of NCPAP or oxygen mask treatment were not documented. We conclude that NCPAP is useful in improving the management of acute respiratory failure in children with DHF/DSS in dengue-endemic areas.

Introduction
Dengue hemorrhagic fever (DHF) is caused by the dengue virus and transmitted by the mosquito Aedes aegypti. Patients with DHF grade 3–4, termed dengue shock syndrome (DSS), may develop acute respiratory failure after initial fluid resuscitation. This manifestation may be due to fluid overload, increased permeability of the alveolar-capillary membrane resulting in oedema in the alveoli and interstitial spaces, acute respiratory distress syndrome (ARDS) or cardiac failure.

The mortality rate of DSS complicated by respiratory failure is very high. Ordinarily, these patients are treated with oxygen through a face mask, or if necessary with tracheal intubation and mechanical ventilation. The high mortality rate may be caused by complications related to mechanical ventilation or due to the treatment being started too late. Continuous positive airway pressure (CPAP) is commonly used in the treatment of restrictive lung diseases, e.g. ARDS, with beneficial results.5

Previously, in an open pilot study, we introduced nasal CPAP (NCPAP) in the management of children with DSS complicated by respiratory failure. It was concluded that NCPAP effectively decreases hypoxemia and contributes to reducing the number of children in need of tracheal intubation and mechanical ventilation.

The purpose of this study was to evaluate the effectiveness of oxygen treatment administered by a face mask vs. NCPAP in pediatric patients with DSS complicated by respiratory failure.

Materials and Methods
An open prospective, randomized controlled study was carried out in children under 15 years of age with DSS complicated by respiratory failure, admitted to the Intensive Care Unit of Pediatric Hospital No. 1 in Ho Chi Minh City, Vietnam from January 1998 to December 1999. The diagnosis of DSS was made according to WHO criteria and confirmed by positive
serodiagnosis. Acute respiratory failure was defined as follows: failure to respond to 40 per cent oxygen by a nasal cannula as evidenced by (1) cyanosis, SaO2 < 93 per cent or PaO2 < 70 mmHg, (2) respiratory rate > 50 breaths/min, or (3) severe chest retraction and nasal flaring. Patients with an immediate need for intubation and mechanical ventilation, epistaxis, coma, or congenital heart disease were excluded. If no CPAP system was available or no informed consent was obtained, the subject was also excluded. Allocation into the two groups of treatment was performed by drawing sealed envelopes that were randomly numbered.

Investigations and observations
On admission the following data were obtained: age, sex, weight, date and grade of shock, type and volume of infused fluid, dengue virus HI, ELISA, and chest X-ray. On admission and after 30 min of treatment respiratory rate, pulse, blood pressure, CVP, arterial blood gas analysis, oxygen flow rate for the oxygen mask group, FiO2 and pressure for the NCPAP group were recorded.

Treatment
The oxygen mask group received oxygen via a face mask with a reservoir bag at a flow rate of 6–8 l/min resulting in an inspired oxygen fraction of 60–80 per cent. In the NCPAP group, a continuous positive airway pressure of 6 cm water delivered through a Beneveniste valve connected to binasal prongs and FiO2 60 per cent was used. Concomitant therapy with intravenous solutions, blood transfusion, vasoactive drugs, diuretics, pleural puncture, and peritoneal paracentesis was instituted in both groups according to the guidelines of the department.

Endpoint
Stabilization of the patient with a PaO2 > 80 mmHg after 30 min of treatment was regarded as a satisfactory endpoint. However, if the condition of the patient deteriorated with hypoxemia (PaO2 < 60 mmHg) and/or respiratory acidosis (PaCO2 > 50 mmHg and abnormal pH) within the first 30 min after inclusion, the study was discontinued and the patient was treated according to the routine procedures of the department. All the patients were followed until oxygen supply via a mask or NCPAP was no longer needed.

Statistics
Data were analysed by SPSS for Windows 9.01. Differences concerning patient characteristics, clinical and paraclinical parameters in the two groups were evaluated using the Student’s t-test and the chi-squared test. All tests were two-sided with differences considered significant at \( p < 0.05 \).

Results
Forty-eight patients were enrolled. Eleven patients were later excluded (two children with DSS complicated by pneumonia, three patients with coma, and six patients with negative serodiagnosis of DHF) limiting the study group to 37 patients. Nineteen patients were assigned to the oxygen mask group and the remaining 18 to the NCPAP group.

On admission there were no significant differences between the groups in terms of age, duration of shock, grading of DHF, elapsed time between onset of symptoms and study entry, pulse, blood pressure, CVP, arterial blood gas values, and chest X-ray (Tables 1 and 2). Conversely, the groups differed significantly concerning sex, weight, the amount of fluid infused prior to inclusion (Table 1), and the respiratory rate on admission (Table 2).

In 92 per cent of the patients chest X-ray revealed pleural effusion. One-third also showed an increased amount of fluid in the interstitial space (Table 1).

After 30 min of treatment the respiratory rate decreased significantly in the NCPAP group (\( p < 0.05 \)), while SaO2 and PaO2 increased in both groups (\( p < 0.01 \)) (Table 2). One patient in the oxygen mask group did not respond to treatment at this time and was consequently given NCPAP with good results. All patients in the NCPAP group responded well to the treatment within the first 30 min of therapy.

Subsequently, 18 patients receiving oxygen mask treatment for more than 30 min, six patients improved further, while the condition of the remaining 12 patients (three with cyanosis and nine with tachypnoe and restlessness) deteriorated in all except one during the next 24 h. The treatment was changed to NCPAP, after which the condition of the patients improved. In the NCPAP group, four out of 18 patients required tracheal intubation and mechanical ventilation during the following 20 h (one due to hypoxemia with PaO2 < 60 mmHg and three with ineffective respiratory pattern) (Fig. 1).

No significant difference between the two groups regarding failure rate after the first 30 min of treatment was noted. However, there was a significantly higher rate of unresponsiveness to treatment in the oxygen mask group compared to the NCPAP group (13/19 vs. 4/18, \( p < 0.01 \)). No significant difference between the two groups regarding infusion of vasoactive drugs was found. Nine patients in the oxygen mask group and 13 in the NCPAP group were given dobutamine 5–10 µg/kg min combined with dopamine 3–7 µg/kg/min, while seven patients in the oxygen mask group and four in the NCPAP group received single dopamine infusion 2–87 µg/kg/min.

In the oxygen mask group peritonal paracentesis was performed in two patients combined with pleural puncture in one of these. In the NCPAP group peritonal paracentesis was performed in five patients, while pleural puncture was done in two patients.
Complications of the NCPAP treatment, such as nose bleeding, pneumothorax or hypotension, were not observed.

The four children in the NCPAP group requiring mechanical ventilation died, all in a condition of multiple organ dysfunction, including gastrointestinal hemorrhage due to disseminated intravascular coagulopathy, hepatic failure and renal insufficiency. All the other patients experienced full recover without sequelae.

**Discussion**

DSS is a pediatric emergency characterized by symptoms of DHF in combination with circulatory failure. The main pathophysiological changes that occur in DHF/DSS include a generalized increase in vascular permeability and haemostasis disorder, resulting in leakage of plasma and hemorrhage. The treatment of DSS involves resuscitation for shock with correction of hypovolemia to restore circulation.
and tissue perfusion. The Intensive Care Unit at Pediatric Hospital No. 1, Ho Chi Minh City annually receives many patients from provincial hospitals with severe or prolonged DSS that do not respond satisfactorily to these standard measures of treatment. These patients are often characterized by respiratory insufficiency.

The etiology of the respiratory failure may be alveolar edema caused by the increased vascular permeability, fluid overload, pleural and peritoneal effusions, acute respiratory distress syndrome (ARDS) or cardiac failure. In our study, mild to moderate pleural effusion was observed on the chest X-ray in 24 patients (65 per cent). The pleural effusion cannot with certainty explain the respiratory insufficiency, because the size of the effusion is not consistent with the severity of the respiratory failure. If hypovolemia is not corrected immediately, the decreased tissue perfusion may result in a condition with multiple organ failure including ARDS. DSS complicated by ARDS was first described in 1995 in a case series comprising three patients. In 1998 Goh, et al. reported that DSS was the third leading cause of ARDS in a pediatric intensive care unit in a dengue endemic area. We found bilateral infiltrations on the chest X-ray in approximately 35 per cent of the patients, consistent in seven cases with ARDS according to the American–European Consensus Conference definition. The remaining six patients showed signs of fluid overload. The condition of all these patients improved after instituting NCPAP treatment. Wali, et al. found a mild to moderate myocardial involvement in young adult patients with DHF/DSS, which could contribute to the respiratory failure seen in DSS patients. The design of our study did not allow us to conclude whether cardiac dysfunction is of importance. Therefore, the respiratory disorder in DHF/DSS patients may be caused by many factors, in which ARDS and fluid overload probably are of importance.

Previously, patients not responding to oxygen supply were treated with nasotracheal intubation and mechanical ventilation leading to a number of complications. NCPAP is a cheap, safe and technologically simple way to provide respiratory support, and is suitable for the treatment of patients with restrictive lung disease, e.g. ARDS. The treatment is known to improve oxygenation in patients with acute respiratory failure by increasing functional residual capacity, redistributing lung water from alveoli to interstitium, optimizing V/Q relationship, and by maintaining the volume of recruited alveoli.

In this study the number of included patients was too small compared with the calculated sample size, due to a decreased number of DHF cases in 1999, which resulted in partly incomparable groups of patients. However, there was a significantly higher failure rate in the oxygen mask group compared with the NCPAP group. Likewise, all the patients that failed to respond to the oxygen treatment, improved after NCPAP treatment was started. Before we introduced NCPAP in our department, it would have been necessary to intubate and ventilate those children not responding to oxygen therapy. This might have resulted in higher morbidity and mortality due to complications including nasal bleeding, ventilator-associated pneumonia and barotrauma. The NCPAP was particularly efficient in the patients with bilateral infiltrations on the chest X-ray, consistent with pulmonary edema or ARDS.

The four patients in the NCPAP group, who required mechanical ventilation, did not differ considerably from the others on inclusion concerning organ dysfunction, but the condition was
characterized by large peritoneal and pleural effusions. The presence of the increased amount of pleural and peritoneal fluid might have caused compression of lung parenchyma and restraint of diaphragmatic movement, which could explain the inefficiency of the NCPAP treatment in these patients.

We conclude that NCPAP is useful in improving the management of acute respiratory failure in children with DHF/DSS. This technologically simple, non-invasive, cheap, and safe way to provide respiratory support is suitable for use in developing countries, where facilities for pediatric intensive care and ventilatory support are inadequate.

References