Noninvasive ventilation for acute respiratory distress in children with central nervous system disorders

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KEYWORDS
Noninvasive ventilation; Neurological and neuromuscular diseases; Central nervous system disorders; Acute respiratory distress; Children

Summary
Background: Acute respiratory distress (ARD) is a relatively frequent occurrence in patients suffering from central nervous system disorders (CNSD) and moderate to severe mental retardation. Whenever conventional therapy is little effective, noninvasive mechanical ventilation (NIV) is the additional treatment in patients with diseases of the peripheral nervous system. However, NIV is traditionally little employed in the acute phase in patients suffering from CNSD. In the latter, either conventional therapy is maintained or invasive mechanical ventilation is instituted if the patient’s condition worsens severely. To challenge the traditional view, we conducted the study to prove that NIV is both applicable and effective in the treatment of ARD also in children with moderate to severe mental retardation.

Methods: We studied 44 children with ARD secondary to pneumonia and CNSD causing moderate to severe mental retardation. The children were divided in two groups. One group received conventional therapy and NIV, the other conventional therapy only, before being advanced to invasive ventilator support when nonresponding. On admission to hospital and one hour following admission we registered pH, PaCO₂, PaO₂, A – a DO₂ and the PaO₂/FiO₂ ratio. The mean hospital stay was also recorded.

Results: After one hour on NIV PaO₂ and pH increased, PaCO₂ decreased, A – a DO₂ and PaO₂/FiO₂ ratio improved. No changes in the above parameters were observed in children on conventional therapy only. Hospital stay was shorter when NIV was instituted.

Conclusions: NIV is both applicable and beneficial in stabilizing blood gases, respiratory and cardiovascular parameters also in children with CNSD. Moreover its use shortens the hospital stay.

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Introduction

Children with central nervous system disorders (CNSD) are at increased risk of acute respiratory distress because they often have compromised pulmonary function and ability to handle secretions, which may, in case of viral infection, result in pneumonia [1]. According to Hollins [2] pneumonia accounts for 77% of deaths of patients admitted to hospital for neurological problems. Recurrent aspiration, ineffective cough reflex, reduced or ineffective mucociliary clearance [3,4] are predisposing factors. Other predisposing factors are deformities of the rib cage such as kyphoscoliosis that reduces the vital capacity [5], or the low sensitivity of central and peripheral chemoreceptors as found in Arnold Chiari disease [6]. Diagnosing acute respiratory distress early enough that noninvasive support would be feasible can be made more challenging if a child’s degree of cognitive impairment severely limits his or her ability to communicate with care providers [7,8]. When mechanical ventilatory support is required, clinicians have traditionally opted to offer endotracheal intubation because of a perceived inability of children with CNSD to tolerate well noninvasive ventilation. Invasive mechanical ventilation has a number of drawbacks and side effects. It requires deep sedation [9,10], exposes to the risk of ventilator-associated pneumonia, extends hospital stay [11–13], and the child can end up ventilator dependent [14,15]. Therefore in many centers invasive mechanical ventilation is instituted only when there is reasonable expectancy that the patient is weaned off the ventilator. As a consequence many children affected by CNSD are denied ventilatory support in case of acute respiratory distress and are treated solely with antibiotics and oxygen delivered via an ordinary device (face mask or nasal cannula). Taking such decisions in an emergency department, weighing institution guidelines against parents’ expectations carries momentous ethical implications [16–19].

There is substantial evidence that noninvasive ventilation (NIV) is safe and effective in the treatment of acute respiratory failure in adults [20] and in children [21]. Therefore, challenging the common attitude we have tested the applicability and effectiveness of NIV in children with CNSD and moderate to severe mental retardation, admitted to a pediatric emergency department for acute respiratory distress from pneumonia.

Methods

This is a prospective nonrandomized nonblinded study. The study protocol, approved by the ethic committee at our institutions, conformed to the ethical guidelines of the 1975 Declaration of Helsinki as revised in 2000 [22].

Patients

We entered in the study 74 children with CNSD with mental retardation regularly followed up at the unit of pediatric neurology of the department of pediatrics of the teaching hospital Vittorio Emanuele in Catania, admitted to the pediatric emergency department, between May 2010 and June 2012 for an episode of acute respiratory distress (i.e. children with CNSD and tachypnea, dyspnea, retractions, grunting, nasal flaring, apnea, altered mental status, pulse oximetry measurement < 90% on room air) according to Bradely et al. [15] secondary to very severe pneumonia, as defined by Scott et al. [23].

In nearly 80% of our patients the etiology of pneumonia was viral. However we could not assert how many suffered from concomitant aspiration pneumonia, that is often associated to the infective form.

Study protocol

On admission to the emergency department of pediatrics, both parents of each child were informed of the availability of NIV and of the traditional objections to its use in patients with moderate to severe mental retardation. Informed consent for the use of NIV was requested and if the option was accepted the child entered the Intervention Group (IG). Children of parents refusing consent to the use of NIV formed the Control Group (CG), Fig. 1.

Causes of exclusion from the study were the presence of: mono or bilateral pleural effusion; PaO2 >60 mmHg and PaCO2 <45 mmHg. mild mental retardation according to International Classification of Functioning Disability and Health — Children & Youth (ICF-CY) [28]. The mental retardation was evaluated on the basis of score for mental retardation (code B117) and score for muscular tone (code B7354) detectable from the medical record of the child. For both tests a score greater than 2 was indicative of the presence of a moderate or severe mental retardation. Appropriateness of the diagnosis of the degree of mental retardation was reassessed individually by two pediatric neurologists by careful examination of patients’ charts.

The children of the control group received a conventional treatment with: aerosol therapy with albuterol, i.v. fluids in amounts adequate to maintain a neutral fluid balance, and i.v. antibiotics according to the guidelines suggested by Esposito et al. [24] and Bradley et al. [25]. Oxygen administration via facial mask was instituted, with fraction of inspired oxygen (FiO2) adequate for the levels of SaO2 (minimum concentration of oxygen that maintains saturations between 88% and 92%) in accord with the guidelines published by Mangera et al. [16].

The children in the intervention group were treated with conventional therapy, as above described, plus noninvasive positive pressure ventilation, with a Bi-Level mode.

For NIV we use a positive inspiratory pressure between 10 and 14 mmHg and positive end-expiratory pressure between 4 and 6 mmHg. The backrest was lifted to an angle of 45°, or the patient was put in a lateral decubitus if unable to sustain a semirecumbent position. A full face mask of adequate size was put in place and Bi-Level NIV started according to British Thoracic Society guidelines [26,27]. Initially the facial mask was hold gently in place by hand and then tightened with tight-fitting securing system when tolerated. Hydrocolloid was used to prevent pressure sores at the bridge of the nose and other points of pressure. The alarm was set monitoring O2 saturation (alarm set for SaO2 < 90%).
On admission continuous monitoring of heart rate (HR) and respiratory rate (RR) were started and blood gas obtained for pH, partial pressure of oxygen (PaO2) and partial pressure of carbon dioxide (Paco2). Concomitantly the alveolar-arterial oxygen gradient (A-a DO2) and the PaO2/FiO2 ratio were also calculated.

A chest X-rays, taken immediately thereafter, was assessed by two radiologists first independently and then in comparison.

After one hour of treatment in both groups blood gas analyses were repeated.

In the study, FiO2 was measured with an Oxygen Analyzer (Oxicheck, Respironics, Philips).

**Objectives of the study**

A preliminary consideration was given to the homogeneity of the study group (IG) and controls (CG). The two groups are compared for, age; sex; central nervous system disorders; score of mental retardation (code B117) and score of muscular tone (code B7354) of the ICF-CY; medications (e.g. inhaled bronchodilators); history of recurrent pulmonary infections with persistent cough, fever and dyspnea; chest physiotherapy; previous episodes of acute respiratory failure; episodes of pneumonia for year; X-ray findings on admission.

Primary endpoint was to evaluate changes of PaO2, Paco2, pH, respiratory rate, heart rate, A—a DO2, and the PaO2/FiO2 ratio:

- in the two groups between the time of admission and after an hour of therapy
- and between the two groups either at admission that after an hour of therapy.

Secondary endpoint was the occurrence of complications possibly secondary to NIV, the number of children in both groups that required the institution of invasive mechanical ventilation at some point, and the length of hospital stay before recovery.

The length of hospital stay was measured by days spent in the semi-intensive ward where the patient was hospitalized after acceptance in the emergency department until the time of discharge or his transfer to the intensive care unit in case it had been required endotracheal intubation and mechanical ventilation.

**Statistical analysis**

For statistical analysis we relied on JMP® 10 program for Mac by SAS Institute. For all variables the approximation to normal of the distribution of the population was tested by Kolmogorov—Smirnov One-Sample Test and statistics for kurtosis and symmetry. Results were symmetrically distributed and were therefore analyzed with the t test for paired data. A p < 0.05 was considered significant.

**Results**

Between May 2010 and June 2012, 74 children suffering from CNSD were seen in the emergency department because of an acute episode of respiratory failure; of these 44 were enrolled in the study and 30 were excluded because they did not meet the inclusion criteria. Twenty-
two accepted the option of a noninvasive ventilatory support and form the intervention group; the remaining 22 form the control group. As shown in Table 1, the intervention and the control groups are fully comparable for age; sex; CNSD; score of mental retardation (code B117) and score of muscular tone (code B7354); medications (e.g. inhaled bronchodilators); history of recurrent pulmonary infections with persistent cough, fever and dyspnea; chest physiotherapy; previous episodes of acute respiratory failure; episodes of pneumonia per year; X-ray findings.

All had fever >38.5 °C, dyspnea, nonproductive cough, respiratory muscles strain, and cyanosis. At physical examination there were severe rales and wheezing.

Blood gases on admission (T0) were consistent with Type 2 respiratory distress in all (Table 2). At T0 there were no statistically significant differences between groups for PaCO₂, PaO₂, pH, A — a DO₂ difference, PaO₂/FiO₂ ratio; heart and respiratory rate (Tables 2 and 3).

After 1 h (T1), in the intervention group all parameters under scrutiny improved significantly: PaCO₂ was reduced (p < 0.0001); PaO₂ increased (p < 0.0001); A — a DO₂ was reduced (p < 0.0001); PaO₂/FiO₂ ratio increased (p < 0.0001). HR and RR were also significantly reduced (p < 0.0001). On the contrary controls did not improve at one hour (Tables 2 and 3); the only significant change was a decrease of respiratory rate (p < 0.0003).

Overall the mean hospital stay was significantly shorter in the intervention group (6.22 ± 1.27 vs 11.63 ± 2.17 days; p < 0.0001; difference = −5.41 Upper CL Diff −4.3187, Lower CL Diff −6.50).

In two additional cases NIV had to be discontinued because of poor patient and family compliance. None of the patients on NIV required invasive mechanical ventilation at any time, while three children in the control group went into progressing desaturation not responding to conservative measures: two had to be started on invasive mechanical ventilation; the parents of the third child refused mechanical ventilation and the patient unfortunately died. Three minor complications secondary to NIV were observed: facial erythema in two children and bridge of the nose ecchymosis in one.

### Table 1: Patients’ characteristics of the two groups treated with (intervention group) or without (control group) non-invasive ventilation.

<table>
<thead>
<tr>
<th>Males/females</th>
<th>Intervention group</th>
<th>Control group</th>
<th>p&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10/12</td>
<td>13/9</td>
<td></td>
</tr>
<tr>
<td>Mean age years</td>
<td>10.18 ± 2.63</td>
<td>8.77 ± 2.67</td>
<td>NS</td>
</tr>
<tr>
<td>Central nervous system disorders (CNSD)</td>
<td>10 SD 7 CM, 3 EE, and 2 L</td>
<td>9 SD 6 CM, 6 EE, and 1 L</td>
<td>NS</td>
</tr>
<tr>
<td>Score for mental retardation (code B117)</td>
<td>3.32 ± 0.48</td>
<td>3.50 ± 0.51</td>
<td>NS</td>
</tr>
<tr>
<td>Score for muscular tone (code B7354)</td>
<td>3.77 ± 0.42</td>
<td>3.95 ± 0.21</td>
<td>NS</td>
</tr>
<tr>
<td>Inhaled bronchodilators prior to admission</td>
<td>22/22</td>
<td>20/22</td>
<td>NS</td>
</tr>
<tr>
<td>Chest physiotherapy</td>
<td>20/22</td>
<td>22/22</td>
<td>NS</td>
</tr>
<tr>
<td>Prior history of episode of acute respiratory failure</td>
<td>12/22</td>
<td>14/22</td>
<td>NS</td>
</tr>
<tr>
<td>Episodes of pneumonia for year</td>
<td>7.22 ± 0.81</td>
<td>7.09 ± 0.75</td>
<td>NS</td>
</tr>
<tr>
<td>Chest radiography in ED</td>
<td>18 ULI; 4 BLI</td>
<td>18 ULI; 4 BLI</td>
<td>NS</td>
</tr>
</tbody>
</table>

SD: spastic diplegia; CM: cerebral malformations; EE: epileptic encephalopathy nonrespondent to pharmacological treatment; L: leukodystrophies; ULI: unilateral lung involvement; BLI: bilateral lung involvement.

| Mean ± standard deviation. |

### Table 2: Blood gas (PaCO₂, PaO₂ and pH) and respiratory parameters (A — a DO₂ and PaO₂/FiO₂) on admission (T0) and after one hour (T1), in the groups treated with (intervention group — IG) or without (control group — CG) non-invasive ventilation.

<table>
<thead>
<tr>
<th>Groups</th>
<th>T0 PaCO₂ mmHg</th>
<th>T1 PaCO₂ mmHg</th>
<th>T0 PaO₂ mmHg</th>
<th>T1 PaO₂ mmHg</th>
<th>T0 pH</th>
<th>T1 pH</th>
<th>T0 A—a DO₂ mmHg</th>
<th>T1 A—a DO₂ mmHg</th>
<th>T0 PaO₂/FiO₂</th>
<th>T1 PaO₂/FiO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>IG T0 vs CG T0</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>IG T0 vs IG T1</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.02</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CG T0 vs CG T1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>IG T1 vs IG T1</td>
<td>0.0001</td>
<td>0.0003</td>
<td>0.014</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</tr>
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</table>
Discussion

Respiratory diseases are the most frequent and serious comorbidities in patients with CNSD [29,30]. Recent studies indicate that NIV is effective in treating episodes of acute respiratory failure in children with diseases of the peripheral nervous system [29,31,32], as NIV increases the functional residual capacity, improves tissue oxygenation, decreases left ventricular postload, and reduces the respiratory muscle work [33]. Indications and management guidelines for NIV have also been published [33,34]. However, guidelines usually stress the difficulties associated with the use of NIV in children with CNSD [34–36]. In this study, we treated acute respiratory distress with NIV in a number of children with CNSD and moderate to severe mental retardation. In all patients, one hour NIV treatment lead to significant improvement of all monitored parameters: \( \text{PaCO}_2 \), \( \text{PaO}_2 \), pH, \( \Delta \text{AEO} \), \( \text{PaO}_2/\text{FiO}_2 \) ratio, while in the control group, no significant changes were observed. The second parameter recording was set at one hour in accord with the reports by several authors that NIV treatment for one hour is sufficient to stabilize acute respiratory distress in children [21,26].

Although conducted on a small cohort, our study demonstrates that NIV can be well tolerated also by children with severe CNS disorders. We think that the poor state of conscience of children with CNSD, further increased by respiratory distress, not only is not an obstacle but may even favor the use of NIV. Recently Scala supported the use of NIV for treatment of acute respiratory failure in hypercapnic encephalopathy syndrome [37] as, just because of the hypercapnic state, the patient is unlikely to resist the ventilator. An additional consideration is that prompt response to NIV as it is commonly observed [38] shortens the time spent in hospital and speeds recovery.

No patients treated with NIV had to be advanced to mechanical ventilation with endotracheal tube, while three children in the control group required mechanical ventilation, but only two families accepted it, while the third died on conventional therapy. In our department, the indication to oro-tracheal intubation for mechanical ventilation is the rapid increase of muscular effort during respiration and the severe difficulty to maintain acceptable levels \( \text{PaO}_2 \) e della \( \text{PaCO}_2 \).

The minor complications associated with NIV were attributable to a selection error of the mask size. In all the symptoms receded after we changed the mask to one more appropriate in size.

Study limitations

As stated previously, the allocation of the patients to the interventional or the control group was not randomized but was determined by the free choice of the parents to grant or refuse consent to treatment with NIV. Lack of randomization carries a risk of bias. And one cannot rule out a difference in treatment at home prior to admission and uneven distribution of preexisting clinical conditions. However, as reported in Table 1, the two groups turned out fully comparable. This can be due in part to the fact that all children were regularly followed in the same rehabilitation center of the same pediatric unit, and the outpatients respiratory problems secondary to their neurological condition are treated according to the very same protocol based on the guidelines set by Wang et al. [39].

As previously stated, in our cohort of children with neuromuscular diseases aspiration pneumonia is frequently associated to infection, either viral or bacterial, and it can be difficult to ascertain which one comes first.

In conclusion, NIV is safe and valuable (stabilizing blood gases and shortening hospital length of stay) in children with CNSD and moderate to severe mental retardation presenting to emergency department with acute respiratory distress due to very severe pneumonia. Its use speeds stabilization and possibly recover from the pulmonary affection. The underlying severe neurological impairment plus the depression of the state of consciousness brought forward by hypercapnia might facilitate NIV compliance instead of being an obstacle as commonly believed.

Conflict of interest

None.
References


