Automatic Tube Compensation as an Adjunct for Weaning in Patients With Severe Neuroparalytic Snake Envenomation Requiring Mechanical Ventilation: A Pilot Randomized Study

Ashutosh N Aggarwal MD DM, Ritesh Agarwal MD DM, and Dheeraj Gupta MD DM

OBJECTIVE: This study aimed to evaluate if the combination of pressure-support ventilation (PSV) and automatic tube compensation (ATC) is superior to PSV alone in weaning patients with severe neurotoxic snake envenoming receiving mechanical ventilation. METHODS: Forty-one patients on volume controlled continuous mandatory ventilation were randomized to weaning with PSV alone (PSV group, 18 patients) or PSV plus ATC (ATC group, 23 patients). In both groups, PSV was initially set at 15 cm H2O, and CPAP at 5 cm H2O, with progressive downward titration. The ATC group additionally, received inspiratory ATC at 100% through a ventilator-software-driven algorithm. The primary outcome measure was weaning duration. Secondary outcomes studied included reintubation rate, occurrence of pneumonia, and hospital mortality. RESULTS: Median time to presentation to hospital after snake bite was 7 hours (interquartile range [IQR] 4–9.5 h). Median duration of weaning was significantly shorter in the ATC group than in the PSV group (8 h, 95% confidence interval 6.6–9.4 h vs 12 h, 95% confidence interval 9.9–14.1 h, \( P \) = .03 via log-rank test). Median duration of mechanical ventilation and intensive-care-unit stay were similar between the PSV and the ATC groups (36.5 h, IQR 23.0–52.0 h vs 41.0 h, IQR 25.0–48.0 h, and 3.5 d, IQR 2–4 d vs 3 d, IQR 2–4 d, respectively). Three patients in the PSV group and none in the ATC group developed pneumonia (\( P \) = .08). No patient in either group needed reintubation or died in hospital. CONCLUSION: The addition of ATC to a standard PSV-based weaning protocol significantly shortened time needed to wean patients with severe neurotoxic snake envenoming, without changing the duration of medical care, morbidity, or mortality. Key words: automatic tube compensation, Elapidae, pressure-support ventilation, snake bites, ventilator weaning. [Respir Care 2009;54(12):1697–1702. © 2009 Daedalus Enterprises]

Introduction

Snake envenoming is a common medical emergency encountered in the tropical countries, and an estimated 35,000–50,000 people die of snake bite every year in India.¹ The bites of elapid snakes cause predominantly neuotoxicity, which manifests as ocular and bulbar paralysis, and paralysis of the muscles of respiration, with resultant respiratory failure.²,³ The management of these patients includes ventilatory support and administration of snake anti-venom. Respiratory failure requiring mechanical ventilatory support is a frequent cause of admission to the intensive care unit (ICU).

Mechanical ventilation is a life-saving intervention, and once there is improvement of the underlying indication, it can be withdrawn abruptly in the majority. However, approximately 20–30% of patients still require gradual discontinuation (ie, weaning).⁴,⁵ This process is not only difficult in patients with chronic respiratory diseases and acute neuromuscular disorders, such as neurotoxic snake bite, but is also associated with important complications, such as nosocomial pneumonia, prolonged ICU stay, and even...
mortality, especially in those with persistent weaning failure.6

In the mechanically ventilated patient, the single greatest cause of imposed work of breathing (WOB) is the resistance caused by the endotracheal tube (ETT).7 Pressure-support ventilation (PSV) is a commonly used maneuver to overcome the ETT resistance.4,5 However, a special mode of ventilatory support called automatic tube compensation (ATC) delivers exactly the amount of pressure necessary to overcome the resistive load imposed by the ETT for the flow measured at the time (so-called variable pressure support).8 This mode therefore unloads the flow-resistant properties of the artificial airway and theoretically can decrease weaning duration and increase the probability of successful extubation by decreasing the WOB.

This pilot study was aimed at evaluating whether a combination of PSV and ATC is superior to PSV alone in weaning patients with severe neurotoxic snake envenoming. We chose these patients as they were unlikely to have any confounding respiratory comorbidities or abnormalities.

Methods

This was a prospective randomized controlled trial conducted in the respiratory ICU of the Postgraduate Institute of Medical Education and Research, Chandigarh, India. The study was approved by the institute’s ethics committee, and written consent was obtained from the next of kin prior to enrollment. In view of the lack of previous outcome data from such patients, all patients requiring respiratory ICU admission for severe neurotoxic snake envenoming between July 2004 and December 2007 were enrolled in this pilot study. The trial was registered at ClinicalTrials.gov (identifier NCT00804011).

Study Participants and Procedure

Patients were included in the study if they met the definition of severe neurotoxic snake envenoming (defined as requirement of mechanical ventilation for ventilatory failure due to snake bite). Snake envenoming was diagnosed based on history of snakebite; presence of fang marks; presence of local manifestations such as swelling, cellulitis, and blister formation; or if the dead snake was brought for identification. Detailed history focusing on time elapsed since bite and onset, and nature of symptoms was recorded for all patients. Complete physical examination, site of bite, local reaction at the bite site, and systemic features were noted. Neuromuscular power was graded as per the Medical Research Council scale.9 All patients underwent arterial blood gas analysis, electrocardiogram, chest radiograph, serum biochemistry (including myocardial-specific creatine phosphokinase), complete blood count, and coagulation profile at initial presentation. Patients received necessary first aid, tetanus prophylaxis, and polyvalent snake anti-venom in standard doses at the emergency services before transfer to the respiratory ICU.

Patients were intubated using ETTs of size 7.5–8.0 mm in women, and 8.0–8.5 mm in men. All patients were mechanically ventilated (Evita 2 Dura ventilator, Dräger Medical, Lubeck, Germany). Initially, volume controlled continuous mandatory ventilation was used. As the neuromuscular paralysis recovered, patients were screened for enrollment thrice a day, as soon as they met the following criteria: (1) substantial improvement in the neuromuscular paralysis, with improvement in grade of power to at least Medical Research Council grade 3; (2) normal sensorium; (3) minimal suctioning requirements (less than thrice in the 8 hours preceding the assessment); (4) no requirement for any vasopressor drugs; (5) no sedation; (6) core temperature less than 38°C; (7) hemoglobin more than 9 g/dL; (8) systolic blood pressure more than 90 mm Hg; and (9) most importantly, overall physician assessment regarding fitness for weaning. The patients meeting the aforementioned criteria were randomly assigned to weaning with PSV alone (PSV group) or PSV with ATC (ATC group). The randomization sequence was computer-generated. The assignments were placed in sealed opaque envelopes, and each patient’s assignment was made on admission to the respiratory ICU by the attending physician. Blinding of treatment allocation was not possible.

Study Interventions

In both the groups the inspiratory pressure was initially set at 15 cm H2O and the expiratory pressure at 5 cm H2O, and titrated to maintain a respiratory rate less than or equal to 30 breaths/min and/or tidal volume 6–8 mL/kg of ideal body weight. In the ATC group, additionally, the size of the ETT was entered into the ventilator software, and patients breathed through the ventilator circuit with inspiratory ATC set at 100%. In both the groups the patients breathed through the ventilator circuit with flow-triggering set at 3 L/min. The inspiratory and expiratory pressures were gradually decreased by 2 cm H2O and 1 cm H2O, respectively, every 30 min to 1 hour. The inspiratory and expiratory pressures were returned to their previous values if the patient was unable to maintain a respiratory rate less than 30 breaths/min or pulse-oximeter oxygen saturation (SPO2) more than 92%. Once the inspiratory pressure was 7 cm H2O, patients were subjected to a T-piece trial for 30 min.6 A short T-piece trial before formal extubation was considered appropriate in this experimental setup, as we were not absolutely certain of the adequacy of our empirical ventilatory settings with reference to weanability. Patients who tolerated the T-piece trial underwent im-
mediate extubation and received supplemental oxygen via air-entrainment mask.

For patients showing poor tolerance to the T-piece trial, full ventilatory support was immediately recommenced. This was defined by a decrease in \( S_{\text{PO}_2} \) to less than 90% while requiring a fraction of inspired oxygen (\( F_{\text{I O}_2} \)) of 0.5; evidence of respiratory distress (respiratory rate \( \geq 35 \) breaths/min in the presence of diaphoresis or thoracoabdominal paradox); sustained increase in heart rate (more than 25% from baseline or \( \geq 140 \) beats/min); or substantial change in systolic blood pressure (\( \geq 180 \) mm Hg or < 90 mm Hg).

Patients following extubation were reinitiated on invasive ventilatory support if they had a respiratory rate more than 30 breaths/min with either hypoxemia (\( S_{\text{PO}_2} \) below 90% for 5 min at an \( F_{\text{I O}_2} \) of 0.5) or presence of hypercapnic acidosis (arterial \( pH < 7.35 \) with \( P_{\text{aCO}_2} \) \( \geq 45 \) mm Hg), or developed stridor with evidence of acute respiratory distress.

**Outcome Variables**

The primary outcome measure was time to successful extubation (ability to maintain spontaneous breathing for 24 hours after extubation) after initiation of the weaning process. The secondary outcome measures were occurrence of pneumonia, reintubation rate, and hospital mortality.

**Statistical Methods**

Statistical analysis was performed (SPSS version 10, SPSS, Chicago, Illinois). Statistical significance was assumed at a \( P \) value of less than .05. Results are presented in a descriptive fashion, as number and percentage, or median and interquartile range. Group differences were analyzed using the Mann-Whitney U test (for continuous variables) and Fisher’s exact test (for categorical variables). Survival curves were constructed to study the effect of weaning strategy on weaning duration using Kaplan-Meier analysis, and group differences were analyzed using the log-rank test.

**Results**

Forty-one patients with severe neurotoxic snake envenoming were randomized to the PSV group (18 patients) or the ATC group (23 patients) during the study period, and data from all participants were available for final analysis (Fig. 1). Snake bite was confirmed by patient report, correlation between clinical manifestations, and recognition of snakes by patients and bystanders. Only 4 dead snakes were brought for identification: all kraits. The exact species was not identified because of the non-availability of venom-specific enzyme immunoassay. There were 29 men and 12 women, ages 13–65 years. There was a considerable delay in instituting definitive care at our institution, as many patients reached the hospital from remote areas. The median interval from time of snake bite to reaching the emergency services at our hospital was 7 hours (Table 1). Further, patients needed manual ventilation with bag-valve-mask resuscitator at the emergency services for a median duration exceeding 5 hours before they could be taken up for mechanical ventilation at our respiratory ICU (see Table 1). One patient (subsequently randomized to the PSV group) suffered cardiac arrest after being brought to emergency services, but was successfully resuscitated. Baseline demographic profile, as well as clinical presentation, was similar in the 2 groups (see Table 1).

The median duration of weaning was, however, significantly shorter in the ATC group than in the PSV group (8 h, 95% confidence interval 6.6–9.4 h vs 12 h, 95% confidence interval 9.9–14.1 h, \( P = .03 \) via log-rank test) (Fig. 2). There were no significant differences in duration of mechanical ventilation, respiratory-ICU stay, or hospital stay between the 2 groups (see Table 1). All patients tolerated the T-piece trial well, and none in either group required reintubation after the first extubation attempt. There were no deaths during the hospital stay in either group (see Table 1). However, one patient in the PSV group had minimal residual neurologic sequelae at hospital discharge, secondary to hypoxic brain damage.

Three patients in the PSV group and none in the ATC group developed pneumonia during hospital stay. Two of them had been on bag-valve-mask ventilation for more than 10 hours and then required mechanical ventilation for 3 days. All the patients with pneumonia responded well to appropriate intravenous antibiotics.
Neurotoxic snake envenoming, occurring mainly due to bites of snakes of the Elapidae family, is one of the most important causes of snake-bite fatality.1 Neuromuscular paralysis in snake bite occurs as a result of blockade of neuromuscular transmission. The earliest manifestation is ptosis, followed by external ophthalmoplegia, with gradual progression to involve other muscles. Respiratory muscles are involved relatively late, with diaphragm being the most resistant.10-12 Management of these patients includes assisted ventilatory support and administration of snake anti-venom. Recently, we have reported our ICU data from 55 patients with severe neurotoxic snake envenoming, in which we evaluated if usage of a higher dosage of snake anti-venom offered any significant clinical advantage over a lower dose, and found no difference between the high-dose and low-dose groups.13

As the basic disease of the patient that necessitated ventilator requirement begins to resolve, all attempts should be placed on removing the ventilator as quickly as possible. Unnecessary delays in this discontinuation process not only increase the hospital stay and patient expenses but also the complication rate from mechanical ventilation (eg, pneumonia, airway trauma). In ICUs in developing countries with limited facilities for ventilatory support, this assumes even greater importance.14 It has been estimated that as much as 42% of the time a medical patient spends on a mechanical ventilator is during the discontinuation process.15 In this study too, several patients needed prolonged manual assisted ventilation after endotracheal intubation, before their transfer and admission to the respiratory ICU. Thus, any intervention that can decrease weaning time or time to extubation in these groups of patients is welcome. It has been suggested that some patients may fail the spontaneous breathing trial because of the increased WOB caused by the presence of an ETT.7 PSV is frequently used to overcome this imposed WOB attributable to artificial airways.16-18 However, when used for this purpose, PSV has several shortcomings. First, the pressure-support level may not accurately match the pressure drop across the ETT.19 For any given breath, pressure support may under-correct for the WOB early in the inspiratory phase when flow is high, and over-correct in the latter part of the inspiratory phase during low flow.7,19-21 Second, setting adequate pressure support may not be as easy or accurate as one might think. The inspiratory trigger, aggressiveness of rise to pressure, and the inspiratory termination criterion can affect synchrony.19,22

### Table 1. Patient Profile and Outcomes

<table>
<thead>
<tr>
<th></th>
<th>PSV Group (n = 18)</th>
<th>ATC Group (n = 23)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Men (n, %)</td>
<td>14 (77.8)</td>
<td>15 (65.2)</td>
<td>.49</td>
</tr>
<tr>
<td>Age (median and IQR y)</td>
<td>26 (24–40)</td>
<td>28 (22–35)</td>
<td>.83</td>
</tr>
<tr>
<td>Time to reach hospital after envenomation (median and IQR h)</td>
<td>5.5 (4.0–9.5)</td>
<td>7.0 (5.0–8.0)</td>
<td>.77</td>
</tr>
<tr>
<td>Duration of bag-valve-mask ventilation before mechanical ventilation (median and IQR h)</td>
<td>5.8 (3.0–10.0)</td>
<td>5.0 (4.0–7.5)</td>
<td>.69</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (median and IQR h)</td>
<td>36.5 (23.0–52.0)</td>
<td>41.0 (25.0–48.0)</td>
<td>.78</td>
</tr>
<tr>
<td>Duration of weaning (median and IQR h)</td>
<td>12.0 (7.0–17.0)</td>
<td>8.0 (7.0–12.0)</td>
<td>.12</td>
</tr>
<tr>
<td>Need for reintubation (n)</td>
<td>0</td>
<td>0</td>
<td>.99</td>
</tr>
<tr>
<td>Respiratory ICU stay (median and IQR d)</td>
<td>3.5 (2.0–4.0)</td>
<td>3.0 (2.0–4.0)</td>
<td>.45</td>
</tr>
<tr>
<td>Hospital stay (median and IQR d)</td>
<td>5.0 (5.0–7.0)</td>
<td>5.0 (4.0–6.0)</td>
<td>.14</td>
</tr>
<tr>
<td>Pneumonia (n, %)</td>
<td>3 (16.7)</td>
<td>0 (0)</td>
<td>.08</td>
</tr>
<tr>
<td>Neurologic sequel (n, %)</td>
<td>1 (5.6)</td>
<td>0 (0)</td>
<td>.44</td>
</tr>
<tr>
<td>Hospital survival (n, %)</td>
<td>18 (100)</td>
<td>23 (100)</td>
<td>.99</td>
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Fig. 2. Duration of weaning in patients receiving automatic tube compensation (ATC) with pressure-support ventilation (PSV) versus PSV alone. The duration of weaning was significantly shorter in the ATC group.

**Discussion**

Neurotoxic snake envenoming, occurring mainly due to bites of snakes of the Elapidae family, is one of the most important causes of snake-bite fatality.1 Neuromuscular paralysis in snake bite occurs as a result of blockade of neuromuscular transmission. The earliest manifestation is ptosis, followed by external ophthalmoplegia, with gradual progression to involve other muscles. Respiratory muscles are involved relatively late, with diaphragm being the most resistant.10-12 Management of these patients includes assisted ventilatory support and administration of snake anti-venom. Recently, we have reported our ICU data from 55 patients with severe neurotoxic snake envenoming, in which we evaluated if usage of a higher dosage of snake anti-venom offered any significant clinical advantage over a lower dose, and found no difference between the high-dose and low-dose groups.13

As the basic disease of the patient that necessitated ventilator requirement begins to resolve, all attempts should be placed on removing the ventilator as quickly as possible. Unnecessary delays in this discontinuation process not only increase the hospital stay and patient expenses but also the complication rate from mechanical ventilation (eg, pneumonia, airway trauma). In ICUs in developing countries with limited facilities for ventilatory support, this assumes even greater importance.14 It has been estimated that as much as 42% of the time a medical patient spends on a mechanical ventilator is during the discontinuation process.15 In this study too, several patients needed prolonged manual assisted ventilation after endotracheal intubation, before their transfer and admission to the respiratory ICU. Thus, any intervention that can decrease weaning time or time to extubation in these groups of patients is welcome. It has been suggested that some patients may fail the spontaneous breathing trial because of the increased WOB caused by the presence of an ETT.7 PSV is frequently used to overcome this imposed WOB attributable to artificial airways.16-18 However, when used for this purpose, PSV has several shortcomings. First, the pressure-support level may not accurately match the pressure drop across the ETT.19 For any given breath, pressure support may under-correct for the WOB early in the inspiratory phase when flow is high, and over-correct in the latter part of the inspiratory phase during low flow.7,19-21 Second, setting adequate pressure support may not be as easy or accurate as one might think. The inspiratory trigger, aggressiveness of rise to pressure, and the inspiratory termination criterion can affect synchrony.19,22 All of these
Factors attempt to match the pressure-support breath to the patient’s varying breathing pattern. Lastly, the user-selected level of pressure support is often not changed from patient to patient with varying ETT size or when higher or lower flow is present, probably resulting in inadequate or excessive support.

ATC is a relatively new ventilatory mode designed specifically to overcome the imposed work of breathing due to artificial airways, and there are some data on its use in several different situations such as chronic respiratory diseases, during surgery, and after cardiac surgery. Studies done in the past have shown that ATC is a good modality for decreasing the WOB by decreasing ETT resistance. Two recent studies have also evaluated the role of ATC in weaning during spontaneous breathing trials. One study randomized 90 patients in a medical ICU to undergo a 2-hour breathing trial with ATC and CPAP of 5 cm H2O, pressure support, or T-tube. Mechanical ventilators equipped with prototype ATC software were used. Patients failing an initial breathing trial subsequently underwent an additional trial with the 2 remaining modes. Half the patients who failed a breathing trial with PSV or T-tube tolerated a subsequent trial with ATC and were successfully extubated. However, the rate of successful extubation was similar with the 3 modes. In the other study, patients were randomized to undergo a 1-hour spontaneous breathing trial with either ATC with CPAP (n = 51) or CPAP alone (n = 48) using the Evita 4 Dura ventilator. Although significantly more patients in the ATC group met the criteria for successful extubation (82% vs 65%, P = .04), there was only a trend for more patients in the ATC group to tolerate the breathing trial and undergo extubation (96% vs 85%, P = .08). Similarly, the rate of reintubation was also not statistically significant (14% in the ATC group and 24% in the CPAP group, P = .28). However, the study did suggest that ATC might be a useful mode for performing a spontaneous breathing trial preceding extubation in a general ICU population. Both these studies have used ATC during spontaneous breathing trials. Even though ATC can be combined with several other ventilatory modes in clinical use, there are hardly any data on such combination modes. A preliminary report had, however, suggested that addition of ATC to PSV can decrease work of breathing by 30–50% (depending on the size of the ETT and the level of pressure support), as compared to PSV alone.

We set the ATC level at 100% support to provide maximal possible compensation for ETT resistance. Unfortunately, there is no published guideline or manufacturer recommendation regarding the level of ATC needed in different clinical situations. A lesser level of ATC might perhaps be useful in tracheostomized patients (where an artificial airway still remains after ventilator disconnection) or for respiratory muscle training in chronically ventilated patients; neither of these was a concern in our patients. We had chosen victims of neurotoxic snake envenomation for this preliminary study, as these patients were likely not to have an abnormal airway and/or lung mechanics that could have confounded our observations. Moreover, the condition is an important cause of neuromuscular weakness requiring ventilatory support at our institute. We found that time needed to wean these patients was less in the ATC than the PSV group, even though the median duration of mechanical ventilation was largely identical in the 2 groups (see Table 1). The reduction in weaning duration, from a median of 12 hours in the PSV group to a median of 8 hours in the ATC group, although small in absolute terms, is statistically and clinically important. In a setup where several patients with respiratory failure need to remain on manual assisted ventilation for prolonged periods before ICU care and mechanical ventilatory support can be arranged, even this small reduction would prove beneficial in the long run. There was, however, no difference in any secondary outcome measure (occurrence of pneumonia, reintubation rate, or hospital mortality). Duration of respiratory ICU and hospital stay was also similar in the 2 groups.

Finally, our study is not without limitations. One obvious limitation is the small sample size. However, this was a pilot study, and the results thus need to be confirmed by studies employing larger number of patients. The other limitation was the lack of blinding, which can potentially introduce a bias. Because our observations were limited to a specific clinical condition, we also cannot comment on the generalizability of our findings to other groups of patients receiving mechanical ventilation.

Conclusions

In conclusion, the results of this study suggest that the addition of ATC to a standard PSV-based weaning protocol can potentially shorten the time needed to wean patients of severe neurotoxic snake envenomation without much influence on the duration of medical care, morbidity, or mortality. More clinical studies are needed to clarify the role of ATC as an adjunct measure in weaning patients off mechanical ventilation.

References