BRIEF REPORT

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Severe weakness complicating status asthmaticus despite minimal duration of neuromuscular paralysis

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Abstract *Objective:* Mechanically ventilated patients with status asthmaticus who undergo prolonged paralysis are at risk for severe weakness due to myopathy. In the mid-1990s, we changed our usual method of achieving tolerance of ventilatory support in asthmatic patients from continuous paralysis to deep sedation. This study examines the impact of this change in practice on the development of clinically significant weakness in status asthmaticus. *Design and setting:* Retrospective cohort study in university-affiliated county hospital. *Patients:* Mechanically ventilated asthmatic patients seen before ($n = 96$) and after ($n = 74$) a clinical practice change in 1995 that markedly restricted use of paralytics. *Results:* The duration of neuromuscular paralysis declined sharply after 1995 (23.7 ± 42.2 vs. 1.8 ± 4.0 h, $P < 0.001$), but this was not associated with a significant difference in the incidence of weakness (21 vs. 14%, $P = 0.23$). Within the post-1995 cohort, there was no significant difference in the duration of paralysis for weak and non-weak patients (3.5 ± 6.2 vs. 1.5 ± 3.5 h, $P = 0.10$). However, weak patients had a much longer duration of mechanical ventilation than did patients without weakness (11.9 ± 3.6 vs. 1.9 ± 1.8 days, $P < 0.001$). *Conclusion:* Mechanically ventilated patients with status asthmaticus who are immobilized for prolonged periods of time by deep sedation remain at risk for clinically significant weakness.

Keywords Muscular diseases ·
Status asthmaticus · Neuromuscular blocking agents · Respiration, artificial

Introduction

Acute myopathy is a known complication of mechanical ventilation for status asthmaticus [1–12]. Several studies, including one by our group [10], have suggested that acute myopathy in status asthmaticus may result from concomitant use of corticosteroids and prolonged neuromuscular paralysis [4–12]. In the mid-1990s, we adopted a policy that encouraged use of deep sedation rather than continuous paralysis to achieve tolerance of ventilatory support, without other substantive changes in management. This study,

the preliminary results of which have been presented previously [13], examines the impact of this change in practice on ICU-acquired weakness in status asthmaticus.

Methods

Patient enrollment

Patients who underwent mechanical ventilation for severe asthma in our medical ICU were divided into

two cohorts: pre-1995 (May 1983–May 1995) ($n = 96$) [10] and post-1995 (May 1995–May 2004) ($n = 74$). None of the patients had severe sepsis, acute renal failure, multi-organ system failure, end-stage liver disease, or a primary diagnosis of chronic obstructive lung disease. Only the first hospitalization was included for patients who were intubated more than once for severe asthma. The study was approved by our institutional review board.

Clinical management (post-1995)

All patients received intravenous methylprednisolone and inhaled bronchodilators (albuterol, ipratroprium). Usual ventilator settings were a tidal volume of 8–9 ml/kg and a respiratory rate of 10–14 breaths/min [14]. Deep sedation (using combinations of propofol, fentanyl, and lorazepam) was used to suppress respiratory drive until there was evidence for a significant reduction in the severity of airflow obstruction, after which sedation was tapered or discontinued to allow a trial of spontaneous ventilation.

Although prolonged paralysis was discouraged, most patients received succinylcholine at the time of intubation and bolus doses of vecuronium or atracurium were sometimes given while sedation was being escalated. We estimated that each bolus of vecuronium or atracurium would provide approximately 30 min of complete paralysis. Continuous paralysis was reserved for those few patients with fulminant airflow obstruction in whom uninterrupted muscle relaxation was deemed necessary.

Outcome definition

Clinically significant weakness was defined as a generalized reduction in muscle strength involving all four limbs that markedly interfered with activities of daily living, and required inpatient physical rehabilitation and/or home physical therapy after hospital discharge [10]. An electromyogram (EMG) was not required for inclusion in the study.

Statistical analysis

Statistical analysis was performed using SPSS version 11.5 (SPSS, Chicago, IL). Descriptive data are presented as mean ± SD except where noted. The Mann–Whitney U test was used to compare continuous variables as these variables were typically not normally distributed. Categorical variables were compared using the Fisher exact test.

Results

Comparison of pre-1995 and post-1995 cohorts

The pre-1995 and post-1995 cohorts did not differ with respect to age (39 ± 17 vs. 38 ± 13 years), gender (56 vs. 45% male), or duration of mechanical ventilation (3.2 ± 4.0 vs. 3.2 ± 4.0 days) ($P > 0.2$ for all comparisons). The percentage of patients who received any neuromuscular blocking agent (NMBA) in the pre-1995 and post-1995 time periods was similar (67 vs. 77%, $P = 0.17$), but the duration of paralysis declined markedly after 1995 (23.7 ± 42.2 vs. 1.8 ± 4.0 h, $P < 0.001$). The incidence of clinically significant weakness in the pre-1995 and post-1995 cohorts was 20 of 96 (21%) and 10 of 74 (14%), respectively ($P = 0.23$).

Comparison of weak and non-weak patients in post-1995 cohort

As expected, EMGs revealed myopathy as the cause of muscle weakness in the six patients who underwent electrophysiologic study [10, 15]. Weak and non-weak patients did not differ with regard to age (40 ± 11 vs. 37 ± 13, $P = 0.34$) or gender (30 vs. 53% male, $P = 0.5$). There was no significant difference in the amount of sedative used for the two groups on the first hospital day, but the cumulative dose of propofol, lorazepam, and fentanyl over the first 3 days was higher in those patients who became weak since many of the non-weak patients had been extubated by day 3 (Table 1). In addition, the dose of methylprednisolone over the first 3 days was higher in those who developed weakness (Table 1).

The duration of mechanical ventilation was markedly longer for weak patients than for those without weakness (11.9 ± 3.6 vs. 1.9 ± 1.8 days, $P < 0.001$) (Table 1). Weak patients were intubated for 7–17 days. The mean duration of paralysis was only slightly longer in those who developed weakness, and did not achieve statistical significance (Table 1).

Chart review was used to determine the reason for prolonged mechanical ventilation in the ten weak patients. One patient developed a nosocomial pneumonia (without sepsis syndrome) that contributed to delayed extubation. In the remaining nine cases, protracted status asthmaticus was the dominant reason for prolonged intubation, with 7–12 days having elapsed before the patients respiratory status was sufficiently improved to allow discontinuation of sedation and a spontaneous breathing trial. Delayed awakening after withdrawal of sedation accounted for an additional 1–3 days of intubation. Respiratory muscle weakness did not appear to contribute to delayed extubation, as evidenced by the fact that once underlying respiratory failure had resolved and the patient was sufficiently awake, spontaneous breathing trials were

Table 1 Clinical parameters depending on presence or absence of muscle weakness

		Weak ($n = 10$)	Not weak ($n = 64$)	P value*
Duration of mechanical ventilation	Mean days $\pm$ SD	11.9 ± 3.6	1.9 ± 1.8	<0.001
Paralytic administration	Any paralytic n (%)	8 (80)	49 (76)	1.0
	Mean duration $\pm$ SD (h)	3.5 ± 6.2	1.5 ± 3.5	0.1
	Median duration (h)	0.8	0.5	
Propofol administration	Any propofol n (%)	9 (90)	57 (89)	1.0
	Mean dose (mg) $\pm$ SD, day 1	$1,472 \pm 1,026$	$1,141 \pm 773$	0.37
	Cumulative dose (mg) $\pm$ SD, days 1–3	$4,684 \pm 2,969$	$1,951 \pm 1,892$	0.005
Lorazepam administration	Any lorazepam n (%)	8 (80)	57 (89)	0.6
	Mean dose (mg) $\pm$ SD, day 1	16.2 ± 30.5	12.7 ± 26.4	0.51
	Cumulative dose (mg) $\pm$ SD, days 1–3	98.3 ± 119	27.5 ± 103	0.04
Fentanyl administration	Any Fentanyl n (%)	8 (80)	22 (34)	0.01
	Mean dose (mcg) $\pm$ SD, day 1	$883 \pm 1,140$	342 ± 729	0.07
	Cumulative dose (mcg) $\pm$ SD, days 1–3	$4,267 \pm 3,765$	$830 \pm 2,074$	<0.001
Methylprednisolone administration	Mean dose (mg) $\pm$ SD, day 1	261 ± 96	205 ± 107	0.06
	Mean daily dose (mg) $\pm$ SD, days 1–3	170 ± 57	$123 + 68$	0.02
Blood glucose (mg/dl)	Mean, highest daily value day 1	182 ± 37	184 ± 78	0.61
	Mean, highest daily value days 1–3	163 ± 23	168 ± 52	0.65

*Mann–Whitney U test for continuous variables; Fisher's exact test for categorical variables

uniformly successful and extubation was accomplished without sequelae (other than a single episode of post-extubation stridor).

Discussion

The principal finding of this study is that mechanically ventilated asthmatic patients who were deeply sedated remained at risk for clinically significant muscle weakness despite a marked reduction in their exposure to neuromuscular paralysis. In the post-1995 cohort, duration of paralysis was similar in weak and non-weak patients. In contrast, the duration of mechanical ventilation was markedly longer for weak patients than for patients without weakness.

Previous studies found an increased risk of acute myopathy in patients with status asthmaticus who underwent prolonged neuromuscular blockade [9–12], but it has been uncertain whether the risk of prolonged paralysis resulted from loss of neuromuscular transmission per se or resultant muscle inactivity. Our findings suggest a role for prolonged muscle inactivity in the development of muscle weakness in status asthmaticus, regardless of whether it is achieved by interruption of neuromuscular transmission or by deep sedation.

The duration of mechanical ventilation was much longer for weak patients than for those without weakness (Table 1), as reported in earlier studies involving patients with asthma or COPD [7, 11, 16]. One possible explanation for this finding is that involvement of the diaphragm could lead to delayed weaning [17, 18]. Alternatively, immobility during prolonged mechanical ventilation could contribute to the development of myopathy. In our previous study, delayed weaning due to respiratory muscle impairment was seen in only 1 of 20 patients [10]. In the present study, prolonged need for mechanical ventilation invariably resulted from slow resolution of airflow obstruction and delayed awakening after use of high-dose benzodiazepine infusions [19]. While the retrospective study design limits our ability to draw firm conclusions regarding the relationship between muscle weakness and prolonged mechanical ventilation, our experience would suggest that in the setting of status asthmaticus, the latter is more likely due to an increased risk of myopathy from prolonged immobility than to delayed weaning from respiratory muscle impairment.

Corticosteroids are believed to be important in the pathogenesis of asthma-related acute myopathy [1–3, 8]. All patients in the current study received relatively high-doses of methylprednisolone, but the amount of corticosteroid given to weak patients was higher than in those without weakness (Table 1). While this likely reflects more severe and persistent airflow obstruction in patients who became weak, a causal role for corticosteroid dose in the development of weakness cannot be excluded. Severe sepsis and multi-organ failure, important risk factors for ICU-acquired weakness in the general critical care population [20], did not occur in the current study and are rare in the setting of status asthmaticus.

There are several important limitations to the present study. First, due to the retrospective and non-randomized study design, we are unable to prove causality between prolonged muscle inactivity and subsequent muscle weakness. Second, the present study dealt specifically with status asthmaticus and its findings may not be

applicable to other conditions in which ICU-acquired weakness occurs. Finally, and most importantly, the results of the present study do not negate the risk of prolonged paralysis in the development of muscle weakness in status asthmaticus. This study was not sufficiently powered to compare the relative risk of prolonged paralysis and deep sedation with regard to muscle weakness, nor did we assess its severity. Indeed, restriction of paralysis was associated with a trend towards less weakness that could conceivably have reached statistical significance with a larger study. However, our data confirms that prolonged paralysis is not a prerequisite for development of severe muscle weakness in patients with status asthmaticus, and suggests that there may be a significant risk of weakness when patients are immobilized by deep sedation for a prolonged period of time.

Conclusion

In conclusion, we found that among patients with severe asthma who underwent mechanical ventilation, clinically significant muscle weakness was not eliminated by changing the method of achieving tolerance of ventilatory support from continuous paralysis to prolonged deep sedation. The most important risk factor for weakness was the duration of mechanical ventilation. This suggests that corticosteroid-treated patients with status asthmaticus who are pharmacologically immobilized for prolonged periods of time are at risk for subsequent weakness, regardless of whether their muscles are rendered inactive by chemical denervation or deep sedation.

Conflict of interest statement The authors have no conflict of interest.

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