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The effect of single-dose and continuous skeletal muscle paralysis on respiratory system compliance in paediatric intensive care patients

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Abstract *Objective:* To investigate the effect of single dose and continuous skeletal muscle paralysis on respiratory system compliance in 53 paediatric intensive care patients.
Design: Prospective clinical study.
Setting: Multidisciplinary paediatric intensive care unit.
Patients: Twenty-three children ventilated for acute pulmonary pathology, and 30 ventilated for isolated intracranial pathology, who initially had normal lungs.
Interventions: The 23 patients with acute pulmonary pathology received a single dose of muscle relaxant to facilitate diagnostic procedures. Fifteen patients with isolated intracranial pathology received continuous skeletal muscle paralysis for longer than 24 h, and the other 15 received no paralysis.
Measurements and results: Respiratory system compliance deteriorated by 14% from 0.519 ± 0.2 to 0.445 ± 0.18 ml cmH_2O^{-1} kg^{-1} ($p < 0.001$) following a single dose of muscle relaxant in the 23 patients with acute pulmonary pathology. In the 15 with isolated intracranial pathology who received continuous skeletal muscle paralysis there was a progressive deterioration in compliance, which reached 50% of the initial compliance by day 4 of paralysis ($p < 0.001$) and improved back to normal following discontinuation of paralysis. There were no changes in compliance in the 15 patients with isolated intracranial pathology who were ventilated but not paralysed. The paralysed patients required mechanical ventilation longer than the non-paralysed patients ($p < 0.001$), and 26% of these patients developed nosocomial pneumonia ($p = 0.03$), a complication that was not seen in the non-paralysed patients.
Conclusions: Skeletal muscle paralysis results in immediate and progressive deterioration of respiratory system compliance and increased incidence of nosocomial pneumonia. The benefits of paralysis should be balanced against the risks of deteriorating pulmonary function.

Keywords Skeletal muscle paralysis · Pulmonary mechanics · Nosocomial pneumonia

Introduction

Skeletal muscle relaxants are widely used in the intensive care setting to facilitate mechanical ventilation, decrease oxygen consumption [1] and decrease fluctuations in intracranial [2] and pulmonary artery pressure. In addition, a single dose of muscle relaxant in conjunction with appropriate analgesia and sedation is

often used to assist in diagnostic procedures in ventilated intensive care patients. The effect of anaesthesia and short-term muscle paralysis on pulmonary mechanics has been well studied in healthy adults [3, 4]; however, it has not been reported in ventilated paediatric intensive care patients with acute lung disease.

Similarly, the effects of continuous skeletal muscle relaxants on lung mechanics has not been fully delineated. A previous study on neonates with acute respiratory failure due to meconium aspiration or respiratory distress syndrome reported a progressive reduction in dynamic compliance during paralysis and significant improvement in pulmonary mechanics when paralysis was discontinued [5]. These results are difficult to interpret in view of the underlying lung disease, which could alter the measurement of compliance.

The purpose of this study was to evaluate the effect of continuous skeletal muscle relaxants on respiratory system mechanics in ventilated paediatric intensive care patients both without underlying lung disease and with acute lung disease.

Materials and methods

A total of 53 ventilated paediatric intensive care patients were studied, aged 3 months–15 years. Of these, 23 were ventilated for acute lung disease and were undergoing diagnostic procedures. Each of these patients had abnormal lung fields on chest radiograph (CXR). The patients were sedated and the ventilation adjusted so that the patients were fully ventilated with little or no spontaneous respiratory effort. A time-cycled pressure-limited mode of ventilation was used. Respiratory system compliance was measured followed by administration of a single dose of 0.15 mg/kg pancuronium to facilitate the procedure. The respiratory system compliance was measured again on the same ventilator settings 10 min after the onset of skeletal muscle relaxation. The diagnostic procedure was then performed on the patient.

The other 30 patients were ventilated for isolated intracranial pathology. Only patients who had normal lungs at the time of initiating mechanical ventilation were included in this part of the study. The lungs were considered normal provided: (1) there was no history of chest trauma or pulmonary symptoms, (2) the initial clinical examination of the chest was normal, (3) the lungs appeared normal on the initial CXR and (4) the initial compliance measurement was greater than 0.6 ml cmH_2O^{-1} kg^{-1}. The patients were volume ventilated with a Siemens servo 900C ventilator (Siemens-Elema, Solna, Sweden) with a tidal volume of 10 ml/kg and 5 cmH_2O PEEP using synchronized intermittent mandatory ventilation. The patients were hand ventilated, and the endotracheal tubes were suctioned at a minimum of four hourly, and all patients received side-to-side postural drainage as part of their routine care. CXRs were performed daily on all the ventilated patients. Continuous skeletal muscle paralysis for a period greater than 24 h was used in 15 of the patients with isolated intracranial pathology and normal lungs. In these patients 0.1 mg/kg pancuronium was given on the first sign of any movement. To ensure sedation and comfort, an infusion of morphine was given. In the other 15 patients no muscle relaxants were used. These patients were also sedated with an infusion of morphine in addition to intermittent midazolam as needed to achieve the required level of sedation and control of intracranial pressure. These patients were initially fully ventilated and were gradually weaned as the patient's neurological status improved. The decision of whether or not to use, and later when to discontinue, paralysis was made by the team of physicians responsible for the patients overall care. One neurosurgical team requested skeletal muscle paralysis for all their patients, and the other team preferred sedation only. All other aspects of care were similar, including the use of intracranial pressure monitoring. The respiratory system compliance was measured daily in all patients until extubation. Any changes in CXR appearance, atelectasis or other complications were noted. The duration of mechanical ventilation and the initial Glasgow Coma Score (GCS) were also recorded.

Measurement of respiratory system compliance in these patients was approved by our hospital's review board and was performed using a passive expiratory flow volume technique [6]. A low dead-space rotatory valve was rotated at peak inspiration causing a brief (200 ms) airway occlusion. Airway occlusion pressure was measured with a Validyne MP 45 pressure transducer. (Validyne Engineering, Northridge Calif.) Passive expiratory flow was measured using a Fleish 1 pneumotachograph connected to a Validyne CD 15 differential pressure transducer. The occlusion pressure and expiratory flow were recorded on an IBM personal computer. Following integration of flow to volume, the passive flow-volume curve was displayed on the screen. Respiratory system compliance was determined by: Crs = V/P ml cmH_2O^{-1} kg^{-1}, were V is the volume extrapolated to zero flow, and P is the occlusion pressure at peak inspiration. Flow volume curves were included if the coefficient of determination of the slope of the expiratory flow volume curve had a regression coefficient of 0.99 or above and covered at least 75% of the expired volume. A minimum of six breaths were analysed, and the mean compliance and standard error were calculated for each set of measurements. The endotracheal tube was suctioned immediately prior to the measurements to remove secretions which may interfere with the measurement. Cuffed endotracheal tubes were used in most patients; in patients with uncuffed endotracheal tubes gentle cricoid pressure was used to eliminate the leak during measurements. Only breaths without spontaneous respiratory activity were measured.

In the 23 patients with acute lung disease the pre- and post-paralysis compliance readings were analysed using paired Student's t test. In the 30 patients with isolated intracranial pathology we performed statistical analysis of variance of the compliance measurements between the paralysis and non-paralysis groups. Post hoc paired Student's t tests with Bonferoni correction for multiple comparisons were used to compare compliance changes within the groups. The non-paired Student's t test with Bonferoni correction for multiple comparisons was used to compare the compliance data between the paralysis and non-paralysis groups in addition to the demographic and clinical data of the two groups. The incidences of atelectasis and nosocomial pneumonia were compared using χ^2 analysis.

Results

The demographic and clinical data of the 23 patients with acute lung disease are presented in Table 1. The compliance deteriorated by 14% from 0.519 ± 0.2 to 0.445 ± 0.18 ml $cmH_2O^{-1}kg^{-1}$ ($p < 0.001$) immediately following the onset of skeletal muscle relaxation. In the patients with more severe lung disease a decrease in compliance of up to 50% was seen. FIO_2 had to be

Table 1 Demographic and clinical data for the patients with acute lung disease who received a single dose of muscle relaxant to facilitate diagnostic procedures.

	Abnormal lungs Single dose relaxant ($n = 23$)
Age (years)	4 ± 4.1
Weight (kg)	15.3 ± 13
Diagnosis (n)	
Adult respiratory distress syndrome	5
Pneumonia	8
Pulmonary contusion	1
Atelectasis following cardiac surgery	9
Diagnostic procedure (n)	
Bronchoalveolar lavage	8
Transoesphageal echocardiography	7
Cardiac catheterisation	2
CAT scan	6
Respiratory system compliance ($ml\,cmH_2O^{-1}\,kg^{-1}$)	
Pre-paralysis	0.519 ± 0.2
Post-paralysis	0.445 ± 0.18*

Values, where not specified, are mean ± SD; * $p < 0.001$

Table 2 Comparison of demographic and clinical data of patients with isolated intracranial pathology who received skeletal muscle relaxants for longer than 24 h (group A) with those patients who received no paralysis (group B).

	Group A ($n = 15$)	Group B ($n = 15$)
Age (years)	7.4 ± 5	7.3 ± 4.2
Weight (kg)	31.6 ± 21	27 ± 16.7
Diagnosis (no. patients)		
Head injury	7	8
Encephalopathy	3	3
Cerebral oedema	2	2
Intracerebral bleed	3	2
Initial glasgow coma score		
Median (range)	6 (5–12)	8 (6–13)
Intracranial pressure monitoring (no. patients)	8	5
Evidence of increased intracranial pressure (no. patients)	3	2
No. days paralysed	3.5 ± 1.2	0
No. days ventilated	5.2 ± 1.9	3.1 ± 1.2*

Values, where not specified, are mean ± SD; * $p < 0.001$

increased in four patients following the onset of skeletal muscle paralysis due to a fall in SpO_2.

Demographic data on the 30 patients ventilated for isolated intracranial pathology are shown in Table 2. Of these, 15 received skeletal muscle relaxants for a period longer than 24 h (group A). The mean duration of paralysis was 3.5 ± 1.2 days (range 2–6 days). The

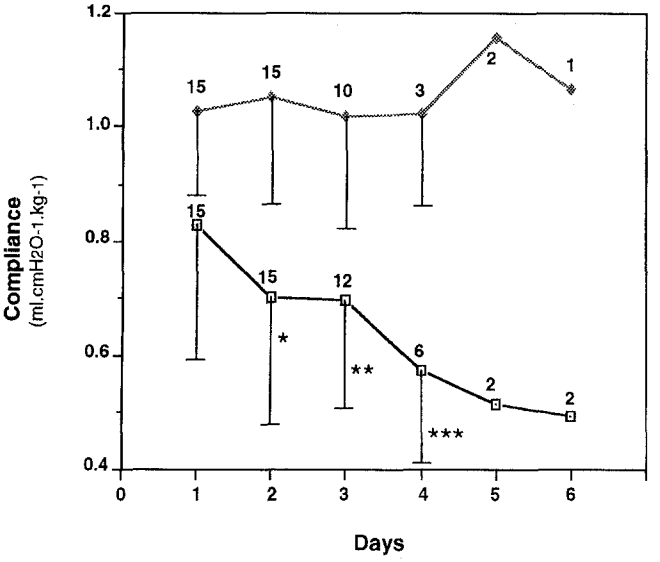

Fig. 1 Change in respiratory system compliance of the 15 patients who received muscle relaxants for longer than 24 h (□) and the 15 patients who received no paralysis (◆). The number of patients remaining in each category on progressive days are indicated. In the paralysed patients compliance deteriorated progressively compared to the non-paralysed patients. No significant change in compliance occurred in the non-paralysed patients. Values are mean ± SD; * $p = 0.005$, ** $p = 0.02$, *** $p = 0.05$

other 15 patients did not receive muscle relaxants (group B). There were no statistically significant differences between groups A and B in age, weight, diagnoses, initial GCS, initial respiratory system compliance, the use of intracranial pressure monitoring or the incidence of raised intracranial pressure. The lowest GCS was 5 in group A and 6 in group B, and none of the patients developed brain death or neurogenic pulmonary oedema.

In the paralysed patients (group A) there was a progressive decrease in respiratory system compliance, which was seen in all 15 patients. The longer the patients remained paralysed, the greater was the fall in compliance, reaching 50% of their initial compliance by day 4 of paralysis (Fig. 1). This decrease in compliance was statistically significant using analysis of variance between the two groups ($p < 0001$), paired t test within the paralysis group on day 2 ($p < 0.001$), day 3 ($p = 0.05$) and day 4 ($p = 0.04$) compared to day 1, and also using the unpaired t test between the two groups on days 2 ($p = 0.005$), 3 ($p = 0.02$) and 4 ($p = 0.05$). Overall compliance fell from 0.830 ± 0.27 to 0.644 ± 0.22 $ml\,cmH_2O^{-1}kg^{-1}$ just prior to discontinuation of paralysis (Fig. 2). This occurred despite regular tracheal toilet and side-to-side postural drainage in all patients. Compliance improved in all 15

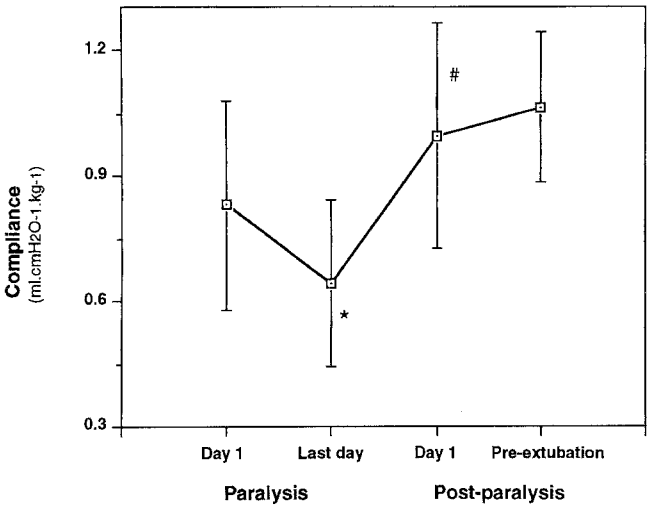

Fig. 2 Change in respiratory system compliance of all 15 patients who received muscle relaxants for longer than 24 h. Compliance deteriorated in all patients during paralysis compared with day 1 of paralysis values and improved following discontinuation of paralysis compared to last day of paralysis values. Values are mean ± SD; $*p < 0.001$, $\#p < 0.001$

patients following discontinuation of paralysis. Overall compliance improved by 54% from 0.644 ± 0.22 ml $cmH_2O^{-1} kg^{-1}$ immediately prior to discontinuation of paralysis to 0.994 ± 0.31 ml $cmH_2O^{-1} kg^{-1}$ 1 day following discontinuation of paralysis ($p < 0.001$; Fig. 2). Many patients required 48 h of chest physiotherapy, coughing and suctioning for the compliance to return to normal. The compliance then remained normal until the patients were extubated and the measurements discontinued. Immediately prior to extubation there was again no significant difference in the compliance measurements of the paralysis and non-paralysis groups, which were 1.004 ± 0.27 and 1.070 ± 0.27 ml $cmH_2O^{-1} kg^{-1}$, respectively. In the 15 patients who did not receive muscle relaxants (group B) there was no significant change in compliance during their period of intubation and ventilation (Fig. 1). No adverse effects on intracranial pressure (ICP) were noted in these patients. There were no significant changes in respiratory system resistance.

Four of the 15 (26.7%) paralysed patients (group A) developed atelectasis on subsequent CXRs, three of whom progressed to nosocomial pneumonia (fever, leukocytosis, and bacteria isolated from culture of the endotracheal tube secretions requiring antibiotic therapy). The atelectasis occurred on day 2 in one patient and on day 3 in the remaining three patients. Complete left lower lobe atelectasis occurred in two patients and complete right lower lobe atelectasis in the other two patients. This complication was not seen in the non-paralysed patients (group B), and the difference between the two groups was statistically significant ($p = 0.03$).

The paralysed patients were also ventilated for a significantly longer period than non-paralysed patients, 5.2 ± 1.9 days vs. 3.1 ± 1.2 days for the non-paralysed group ($p < 0.001$). Similar ventilator rates, PEEP and tidal volumes were used to ventilate the two intracranial pathology groups. The initial ventilator rates for the paralysed patients were 16 ± 3.7 breaths per minute and for the non-paralysed patients 14.2 ± 2.9 breaths per minute. The resultant inspiratory pressures in the paralysed patients were significantly higher, 27 ± 12 vs. 23 ± 8 cmH_2O in the non-paralysed patients ($p = 0.01$). All 30 patients with intracranial pathology survived and were discharged from the intensive care unit.

Discussion

In our paralysed patients with acute lung disease, respiratory system compliance decreased immediately following the onset of skeletal muscle relaxation. This is similar to the adult patients with normal lungs reported by Howell and Peckett [3] and Douglas et al. [4], where lung compliance also decreased following anaesthesia and paralysis. Miller et al. [7] noted a 28% decrease in functional residual capacity and a 29% decrease in arterial-to-alveolar oxygen ratio in nine infants with hyaline membrane disease immediately following the onset of skeletal muscle paralysis. They postulated that the alveolar derecruitment resulted from the loss of expiratory braking mechanisms of the diaphragm and intercostal muscles. There are benefits in using muscle relaxants to facilitate procedures, such as a decreased likelihood of accidental extubation; however, this must be balance against the risks of deteriorating pulmonary function.

In our paralysed patients with isolated intracranial pathology, respiratory system compliance decreased progressively during the period of paralysis and improved on discontinuation of paralysis. This occurred despite these patients having normal lungs at the commencement of mechanical ventilation and receiving regular tracheal suctioning and side-to-side postural drainage. A similar decrease in dynamic compliance was observed by Bhutani et al. [5] in paralysed infants ventilated for acute respiratory failure due to meconium aspiration or respiratory distress syndrome. He also noted improvement in compliance following discontinuation of paralysis in these infants. Thus,

these changes in lung mechanics occur in normal as well as abnormal lungs.

The observed immediate decrease in respiratory system compliance may be due to the effect of muscle paralysis on the position and motion of the diaphragm. Using a radiological technique, Froese and Bryan [8] found that neuromuscular blockade caused a cephalad shift in the end-expiratory position of the diaphragm and a reversal in the pattern of diaphragmatic displacement. The diaphragm was displaced cephalad by the intra-abdominal pressure, and during ventilator inspiration the passive diaphragm was displaced preferentially in non-dependent zones where abdominal pressure is least, whereas during spontaneous respiration the greatest diaphragm displacement occurred in the dependent zones. The decrease in lung compliance and altered diaphragm mechanics could not be fully reversed by the use of PEEP [8] or larger tidal volumes [4]. This altered diaphragm mechanics, in addition to progressive secretion retention due to inhibition of coughing and decreased interstitial fluid clearance from the lung and chest wall may also explain the progressive deterioration in compliance observed in our patients following the use of continuous skeletal muscle paralysis. The inhibition of coughing results in progressive secretion retention which leads to microatelectasis. In 27% of our paralysed patients this progressed to lobar atelectasis and nosocomial pneumonia. The period of mechanical ventilation was also significantly longer in the paralysed than in the non-paralysed patients. Other potential risks of the prolonged use of muscle relaxants such as accidental ventilator disconnection, persistent muscular weakness [9;10] and awareness [11] were not seen in our patients.

Although this was not a randomised study, we feel that our paralysis and non-paralysis groups were comparable. There were no statistically significant differences in patient demography or in clinical data between the two groups regarding initial GCS, incidence of ICP monitoring, raised ICP and initial respiratory system compliance. The longer period of mechanical ventilation required in the paralysed patients may have been due to the adverse effects of the muscle paralysis on the lung mechanics. The initial compliance measurements, although not statistically different, were lower in the paralysed patients. These patients were often transferred to our intensive care unit from other hospitals after having already been paralysed for several hours during transport.

Howell [3] found that a 30% decrease in lung compliance occurs immediately when normal subjects are anaesthetised and paralysed. Thus compliance may have already decreased from the initial value by the time that the first compliance measurement could be made at our hospital. This is supported by our observation that compliance returned to a value 20% greater than the initial paralysis values on discontinuation of muscle relaxants.

Hsiang et al. [12] recently reviewed 514 severely head injured patients from four trauma centres and noted that the patients who were pharmacologically muscle relaxed had a significantly longer intensive care stay and a higher incidence of pneumonia. Although there were more survivors amongst the paralysed patients, there were significantly more vegetative or severely disabled survivors than amongst the non-paralysed patients. They suggested that the use of neuromuscular blockade should be reserved for patients with intracranial hypertension who require escalation of treatment intensity. Our muscle-relaxed patients similarly required a longer period of mechanical ventilation and had a higher incidence of pneumonia. However, all of our patients survived and were discharged from the intensive care unit.

In conclusion, there was an immediate deterioration in respiratory system compliance in the patients with acute lung disease following a single dose of muscle relaxant. In the patients paralysed for longer than 24 h there was a progressive deterioration in respiratory system compliance which returned to normal on discontinuation of muscle paralysis. The patients receiving continuous skeletal muscle paralysis developed significantly more nosocomial pneumonia and required longer periods of mechanical ventilation than the non-paralysed patients. Thus, during the use of muscle relaxants the benefits of continued paralysis should be balanced against the risks of deteriorating pulmonary function.

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