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Continuous infusion of ketamine in mechanically ventilated children with refractory bronchospasm

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Abstract *Objective:* To determine whether ketamine infusion to mechanically ventilated children with refractory bronchospasm is beneficial.
Design: Retrospective chart review.
Setting: Pediatric intensive care unit (PICU) of a children's hospital.
Patients: Seventeen patients, ages ranging from 5 months to 17 years (mean 6±5.7 years), were admitted to our PICU over a 3-year period and received ketamine infusion during a course of mechanical ventilation. The patients had acute respiratory failure associated with severe bronchospasm due to status asthmaticus ($n = 11$), bronchiolitis caused by respiratory syncytial virus ($n = 4$), and bacterial pneumonia ($n = 2$).
Interventions: All patients had been mechanically ventilated for 1–5 days (2.2±1.5 days) and received conventional treatment to relieve bronchospasm for more than 24 h prior to the initiation of ketamine treatment. An intravenous bolus of ketamine of 2 mg/kg, followed by continuous infusions of 20–60 μg/kg per minute (32±10 μg/kg per minute) was administered to all patients without changing their preexisting bronchodilatory regimen. Benzodiazepines were also given intravenously to all patients during the ketamine treatment.
Measurements and main results: The PaO_2/FIO_2 ratio in all patients ($n = 17$) and the dynamic compliance in the volume-preset mechanically ventilated patients ($n = 12$) were calculated. The PaO_2/FIO_2 ratio increased significantly from 116±55 before ketamine, to 174±82, 269±151, and 248±124 at 1, 8, and 24 h respectively, after the initiation of the ketamine infusion ($p < 0.0001$). Dynamic compliance increased from 5.78±2.8 cm^3/cmH_2O to 7.05±3.39, 7.29±3.37, and 8.58±3.69, respectively ($p < 0.0001$). $PaCO_2$ and peak inspiratory pressure followed a similar trend of improvement with ketamine administration. The mean duration of the ketamine infusion was 40±31 h. One patient required glycopyrrolate 0.4 mg/day to control excessive airway secretions and one patient required an additional dose of diazepam to control hallucinations while emerging from ketamine. All patients were successfully weaned from mechanical ventilation and discharged from the PICU.
Conclusion: Continuous infusion of ketamine to mechanically ventilated patients with refractory bronchospasm significantly improves gas exchange and dynamic compliance of the chest.

Key words Ketamine infusion · Asthma · Bronchiolitis · Bronchospasm · Dynamic compliance · Oxygenation

Introduction

Mechanical ventilation of patients with severe airway resistance and poor chest compliance, as in asthma, is often difficult [1, 2]. Despite proper sedation, neuromuscular blockade, and aggressive bronchodilatory therapy, adequate gas exchange may not be attained in these patients and barotrauma from high mechanical inspiratory pressures may occur [3, 4]. Administration of ketamine to asthmatic patients has been shown to result in diminished bronchospasm [5, 6]. When given to mechanically ventilated adult patients with refractory bronchospasm, a marked improvement in chest compliance has also been observed [7]. Since ketamine is a potent sedative which can be administered by continuous infusion to critically ill pediatric patients [8], its administration can provide both beneficial effects, sedation and bronchodilation. However, recognition of the potential complications of this treatment is mandatory. The emergence phenomena, excessive tracheobronchial secretions, and the cardiovascular effects may be hazardous [9], but are easily preventable or manageable by a knowledgeable and skillful care provider.

Over a 3-year period, we employed a treatment protocol utilizing continuous infusion of ketamine for mechanically ventilated children with severe refractory bronchospasm. Our goal in this retrospective study was to assess the efficacy of this treatment and its effects on dynamic compliance and gas exchange.

Patients and methods

The medical records of all patients who had received continuous ketamine infusion for severe bronchospasm during mechanical ventilation in our pediatric intensive care unit (PICU) over a 3-year period were reviewed. The clinical data collected included demographic data, diagnoses, mode and duration of mechanical ventilation, and the dose and duration of the ketamine treatment. We calculated the (partial oxygen pressure) PaO_2/(fraction of inspired oxygen) FIO_2 ratio for all patients, and the dynamic compliance (DC = TV/(PIP-PEEP), where TV = tidal volume, PIP = peak inspiratory pressure, and PEEP = positive end expiratory pressure) for patients who received volume-preset mechanical ventilation, before and during the first 24 h of ketamine administration. Adverse effects of this treatment were also documented.

We planned to collect and analyze data only from patients in whom the bronchodilatory treatments given prior to the ketamine treatment, as well as the ventilator settings, remained unchanged during the first 24 h following the initiation of the ketamine infusion. In addition, patients in whom additional new bronchodilatory treatments had been introduced during the first 24 h of ketamine infusion were not included in the study.

The data are presented as the mean±SD in the text and as the mean±SEM in the figure. We employed one-way analysis of variance for repeated measures and the multiple comparison method of Bonferroni to identify significant changes between the pre- and post-ketamine values. We rejected the null hypothesis at $p<0.05$.

Results

Over a 3-year period, 17 patients were suitable for data collection and analysis. All patients were admitted to the PICU and received ketamine infusion for severe bronchospasm during a course of mechanical ventilation. All patients had received, prior to the initiation of ketamine infusion, continuous albuterol inhalation treatment at a dose ranging from 0.15 to 0.45 mg/kg per hour and daily intravenous methylprednisolone at 4 mg/kg divided into 4 doses. Three patients received continuous theophylline infusion at a dose ranging between 0.9 and 1.1 mg/kg per hour in addition to albuterol and methylprednisolone, and had levels within the therapeutic range (10–20 mg/l). Two other patients received continuous infusion with terbutaline at 2 mg/kg per hour in addition to albuterol and methylprednisolone.

Eleven patients had severe status asthmaticus, four had respiratory syncytial virus (RSV) bronchiolitis and two had bacterial pneumonia. The patients had been mechanically ventilated for a mean of 2.2±1.5 days before ketamine treatment was started. All patients were paralyzed with either pancuronium or vecuronium and received only benzodiazepines for sedation in addition to ketamine (Table 1). Mechanical ventilation was guided by our permissive hypercapnia protocol, i.e., patients on volume-preset mechanical ventilation received a tidal volume that generates PIP of less than 40 cmH_2O. Similarly, patients on pressure-preset mechanical ventilation received PIP less than 40 cmH_2O. We abide by the protocol guidelines, as long as the resulting hypercapnia is not associated with a pH less than 7.28. Our goal is to achieve adequate oxygenation (PaO_2 65–70 torr or O_2 saturation 90–95%) with the minimal possible FIO_2. Volume-preset mechanical ventilation was used in 12 patients (PB 7200, Puritan Bennett, Overland Park, Kan.) and the DC and the PaO_2/FIO_2 ratio were calculated. In five pa-

Table 1 Clinical data ($n = 17$)

Variable	Mean	SD	Range
Age in years	6	5.7	0.5–17
Days on mechanical ventilation prior to initiation of ketamine treatment	2.2	1.5	1–5
Ketamine infusion			
Dose of ketamine after 2 mg/kg bolus (μg/kg per minute)	32	10	20–60
Duration of ketamine infusion (h)	40	31	12–96
Additional sedation			
Dose of midazolam (μg/kg per minute) after 100 μg/kg bolus ($n = 11$)	3.8	1.4	2–6
Daily diazepam dose (mg/kg) divided into six dose ($n = 6$)	1.2	–	–

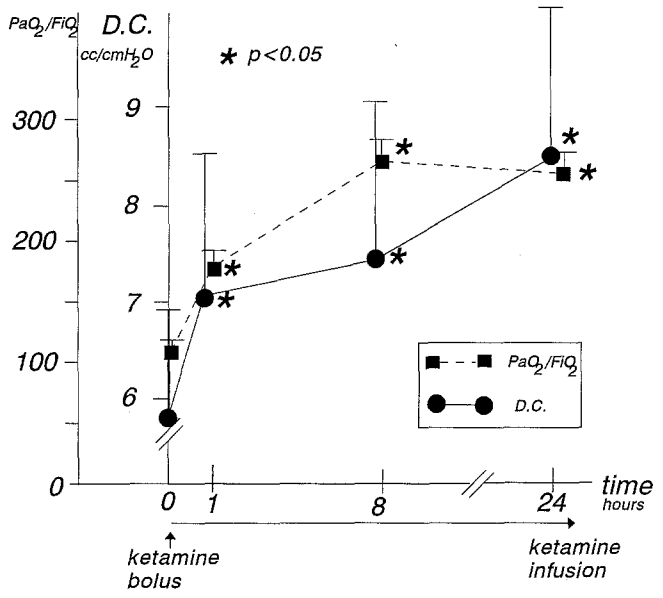

Fig. 1 The temporal changes in PaO_2/FIO_2 ratio and dynamic compliance (D.C.) following the initiation of ketamine treatment and during the first 24 h thereafter. Values at time 0 represent values immediately prior to (no earlier than 1 h) ketamine administration. An *asterisk* denotes a significant change compared to time 0 ($p<0.05$)

tients, pressure-preset mechanical ventilation was used and, thus, only PaO_2/FIO_2 was calculated.

The patients' DC and PaO_2/FIO_2 ratio improved significantly within 1 h after initiation of ketamine, and the improvement persisted (Table 2, Fig. 1). The $PaCO_2$ and PIP values followed the same trend (Table 2). Clinically, the patients with RSV and bacterial pneumonia responded to ketamine not differently from those with asthma.

Adverse effects were noted in two patients: one had excessive tracheobronchial secretions which had not been observed prior to the ketamine treatment, and another experienced hallucinations as an emergence phenomenon. These adverse effects were successfully treated, the former with glycopyrrolate 0.4 mg/day (in four divided doses) during the ketamine infusion period, and the latter with a diazepam bolus of 0.2 mg/kg. None of the patients studied demonstrated any significant change in their heart rate or blood pressure that required treatment. All patients were successfully weaned from mechanical ventilation and discharged from the PICU.

Discussion

Ketamine is a potent anesthetic which can be administered intravenously, intramuscularly, and even orally [10]. The drug induces a dissociation between the thalamoneocortical and limbic systems, providing sedation, amnesia, and analgesia [9]. It can be used safely for intraoperative anesthesia and postoperative sedation. Its metabolism occurs primarily in the liver where it is converted to norketamine by N-methylation [11]. Children appear to metabolize ketamine more rapidly, with a half-life of 1–2 h [9].

Previous studies have shown that ketamine administration induces endogenous catecholamine release [12]. This explains the dose-related increase in heart rate and blood pressure in treated patients with normal myocardial function, as well as the relief of bronchospasm in asthmatic patients. Thus, the administration of ketamine to induce anesthesia and facilitate endotracheal intubation in patients with bronchospasm has become common practice [11]. When mechanical ventilation is instituted for these patients, appropriate sedation, with or without neuromuscular blockade, is also mandatory to assure that adequate gas exchange is not disrupted [13]. All of our patients were mechanically ventilated, pharmacologically paralyzed, and unresponsive to the bronchodilatory management administered prior to ketamine treatment.

To determine the degree of improvement in the patients' gas exchange resulting from ketamine administration, we elected to evaluate the trend in the PaO_2/FIO_2 ratio. This ratio is a commonly used index for oxygenation, reflecting the severity of respiratory illness [14]. We also followed the trend of the patients' $PaCO_2$ values, as ventilation indices have not yet been commonly accepted. The PaO_2/FIO_2 ratio in our patients had been 116±55 before ketamine treatment was started. This low ratio indicates that high, potentially toxic, concentrations of oxygen had to be administered to the patients to prevent

Table 2 Respiratory data (*DC* dynamic compliance, *TV* tidal volume, *PIP* peak inspiratory pressure, *PEEP* positive end expiratory pressure)

Variable	Preketamine	Postketamine			p*
	1 h	1 h	8 h	24 h	
PIP (cmH_2O)	58±17	44±14	38±12	33±10	<0.01
DC = TV/(PIP-PEEP) (cm^3/cmH_2O) (n = 12)	5.78±2.8	7.05±3.39	7.29±3.37	8.58±3.69	<0.01
PaO_2/FIO_2	116±55	174±82	269±151	248±124	<0.01
$PaCO_2$ (torr)	59.8±9.9	43.4±4.3	37.9±4.2	38.7±4.4	<0.01

*$p<0.01$ indicates a significant change in all postketamine values compared to baseline

hypoxemia. The fact that within 1 h after ketamine administration had been initiated this ratio as well as the $PaCO_2$ improved, suggests a cause and effect relationship between ketamine and the improved pulmonary gas exchange in our patients.

The volume-pressure relationship during mechanical ventilation is called the dynamic compliance. The DC represents the flow-dependent, or resistive pressure, changes in the respiratory system [15, 16]. The lower the DC, the more significant the airway obstruction. In a patient with reactive airway disease, a decrease in DC would mean more severe bronchospasm, and vice versa. In all of our patients, the DC increased significantly within 1 h after initiation of ketamine treatment. This trend of improvement continued throughout the 24-h study period. PIP, the main determinant of DC, followed a similar trend of improvement. That this beneficial effect on DC was, again, observed so close in time after initiation of ketamine treatment, strongly suggests that it was primarily the ketamine administration which improved the bronchospasm and thereby improved chest compliance in our patients, and not any of the other ongoing treatments.

Although the etiology of the bronchospasm in our patients was not uniform, we could not detect any clinical difference in the response to ketamine by our three groups of patients. Bronchospasm is the response of the bronchial system to offending stimuli and substances, including allergens, inflammation, infection, and foreign body aspiration. It is, therefore, not uncommon to encounter patients with RSV pneumonitis and bacterial pneumonia who develop refractory bronchospasm. The favorable response to ketamine, by all of our patients, indicates that this treatment can be used in mechanically ventilated patients with bronchospasm of various etiologies.

The clinician who elects to administer ketamine to the critically ill patient in the ICU setting has to be adept in identifying and managing its side effects. Ketamine increases salivary and bronchial gland secretion through stimulation of central cholinergic receptors [17]. Concomitant administration of an anticholinergic drug is, therefore, recommended. This side effect was encountered in only one of our patients, and was easily controlled by daily administration of glycopyrrolate in four divided doses. Emergence phenomena or hallucinations have commonly been observed with ketamine treatment, but are effectively prevented or treated with benzodiazepines [11]. In our experience, the concomitant use of continuous infusions of midazolam or intermittent boluses of diazepam effectively reduced the incidence of this side effect, as only one of our 17 patients experienced it. Ketamine can also cause tachycardia and hypertension, possibly via an endogenous release of catecholamines [18]. This side effect was not observed in any of our patients; however, when it exists it may be deleterious. Other side effects, such as a possible increase in intracranial pressure [19] and an increase in pulmonary vascular resistance [20] may be of concern in patients with brain insults and congenital cardiac defects, respectively, but seem to be inapplicable to the patient population described in our study.

Inhalational anesthetics, halothane in particular, have been advocated in patients with refractory bronchospasm [21]. Halothane appears to be a very potent bronchodilator and is considered the inhalational anesthetic of choice for patients with asthma who have to undergo surgical procedures [22]. However, most PICUs may not be set up for this mode of therapy, and transferring critically ill patients to the operating suite may be too risky. The advantage of an intravenous anesthetic, such as ketamine, is that it can be administered in most ICU settings and does not require specific anesthesia equipment, in contrast to inhalational anesthetics.

In summary, mechanically ventilated pediatric patients with refractory bronchospasm respond to the continuous infusion of ketamine within 1 h after its initiation, showing a significant improvement in their dynamic compliance and oxygenation. The side effects of this treatment appear to be minimal and easily controllable.

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