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PEDIATRIC BRIEF REPORT

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Isoflurane therapy for severe refractory status asthmaticus in children

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Abstract *Objective:* To describe the use of inhaled isoflurane in a series of children with life-threatening asthma. *Design:* Retrospective case series. *Setting:* Pediatric intensive care unit of a tertiary-care children's hospital. Ten children ranging in age from 1 to 16 years with 11 episodes of severe asthma requiring invasive mechanical ventilation in the pediatric intensive care unit over a 5-year period. *Results:* Isoflurane resulted in an improvement in arterial pH and a reduction in partial pressure of arterial carbon dioxide ($PaCO_2$) in all the 11 instances. This effect was sustained in 10 cases and led to clinical improvement and rapid weaning from mechanical ventilation. One child failed to show sustained response and was placed on veno-venous extracorporeal membrane oxygenation. One child died secondary to anoxic brain injury sustained prior to hospitalization. Hypotension was the major side effect, and occurred in 8 children necessitating vasopressor support. *Conclusions:* Isoflurane improves arterial pH and reduces partial pressure of arterial carbon dioxide in mechanically ventilated children with life-threatening status asthmaticus who are not responsive to conventional management.

Keywords Respiratory failure · Status asthmaticus · Pediatrics · Isoflurane

Introduction

The prevalence of childhood asthma and the resultant mortality continues to rise despite many advances in prevention and treatment [1, 2]. Acute respiratory failure necessitating mechanical ventilation is a rare but life-threatening complication of asthma [3]. The increased use of non-invasive ventilation for acute exacerbation of asthma in recent years has further decreased the need for endotracheal intubation and mechanical ventilation in a child with status asthmaticus [4, 5, 6]. Nevertheless, positive pressure mechanical ventilation can be a challenging treatment modality in children with status asthmaticus. High peak airway pressures and dynamic hyperinflation often lead to barotrauma, pulmonary air leaks and hemodynamic compromise [3, 7, 8].

Isoflurane, an inhalational anesthetic agent with bronchodilating properties, has been used in patients with severe catastrophic asthma exacerbations refractory to conventional therapy [9, 10, 11, 12, 13]. We describe our experience with use of isoflurane in 11 episodes of life-threatening acute asthma in children over a 5-year period in the intensive care unit (ICU) of a tertiary-care children's hospital.

Methods

Medical records of children with refractory status asthmaticus who were administered isoflurane over a 5-year period were identified and reviewed. Details of demographic information, medical history, pharmacological agents used, blood gas parameters and the dose and duration of isoflurane administered were collected. Sequential pH and $PaCO_2$ were analyzed. Clinical outcomes measured included duration of mechanical ventilation,

use of vasoactive agents and survival. Information about adverse outcomes including air leaks, hypotension and secondary infectious complications was collected and analyzed.

All the children were managed at a tertiary-care pediatric ICU located in a university-based children's hospital. Mechanical ventilation was instituted using a Siemens Servo 300 ventilator (Maquet Critical Care, Bridgewater, NJ, USA). Mechanical ventilation strategies aimed at limiting barotrauma, maintaining optimal oxygenation and permitting hypercapnia. These strategies included pressure-limited ventilation mode with low tidal volumes (5–8 ml/kg), long expiratory time and low ventilatory rates. All patients received maximal conventional medical management that included continuous inhalation and intravenous infusion of beta agonists, methyl-xanthine infusions, high-dose intravenous steroids and in a few cases ipratropium bromide inhalation, magnesium sulfate and ketamine infusion.

Patients who continued to show progressive deterioration despite conventional treatment and manifested worsening respiratory acidosis (arterial $pH \leq 7.25$) or hypercapnia ($PaCO_2 > 80$) and clinically observed poor air entry with peak inspiratory pressures of $> 45\ cmH_2O$ were considered candidates for isoflurane inhalation (Fig. 1). At our institution, sodium bicarbonate is not routinely administered in children with respiratory acidosis irrespective of the arterial pH, the lone exception being presence of myocardial dysfunction or persistent arrhythmias. The physician team taking care of the patient made the individual treatment decisions following the general management guidelines.

Isoflurane was administered using a Siemens Servo 900 C Ventilator with Siemens ISO Vaporizer 952 (Maquet Critical Care) attached to the low-pressure inlet. The inhaled and exhaled gases were analyzed for CO_2, O_2 and isoflurane using a dedicated Ohmeda Rascal II Mass Spectrometer (Datex-Ohmeda, Helsinki, Finland). A non-rebreathing ventilator circuit with a standard anesthesia scavenging system was used by connecting the exhaust port of the ventilator to a T-piece attached to a 3-l reservoir bag. Wall suction was applied to the remaining limb of the T-piece until the reservoir bag was partially filled with each breath, but never fully collapsed. Exhaled gases were completely scavenged through this system and any leaks were readily detected due to the characteristic pungent odor of isoflurane. An in-house pediatric intensivist in collaboration with the pediatric anesthesiologist supervised the administration of isoflurane.

Isoflurane concentration was increased progressively to a maximum of 2% till either clinical or laboratory improvement in minute ventilation was evident or significant hypotension was encountered. Continuous albuterol administration was discontinued during the administration of isoflurane due to concerns regarding drug interactions between isoflurane and nebulized albuterol and the possibility of immeasurable dilution of isoflurane by nebulizer gas flow. However, intermittent albuterol was administered using a metered dose inhaler connected to the inspiratory limb.

Most children on mechanical ventilation were already receiving infusions of fentanyl and midazolam prior to the initiation of isoflurane. In addition, ketamine infusion was continued in cases where the children were receiving this drug prior to isoflurane therapy. Many children who received greater than 1% isoflurane often did not exhibit any need for additional sedatives. Additional opioids were always administered prior to any painful procedures. Most children received neuromuscular blocking agent (vecuronium or doxicurium) to prevent ventilator–patient dyssynchrony.

High-dose intravenous steroids (2–4 mg/kg/day of methyl prednisolone) were continued for 4–6 days in all the children. Vasopressors and inotropes were added if boluses of crystalloids were ineffective in restoring adequate systemic blood pressure. The choice of specific vasoactive agent and its timing was made by the individual physicians taking care of the child. Renal and liver functions were monitored on a daily basis.

Patients were weaned off isoflurane once they demonstrated a sustained clinical and laboratory improvement in their ventilatory status. If the arterial pH was > 7.25 and rising, the $PaCO_2 < 80$ torr, and the peak inspiratory pressure was $< 35\ cmH_2O$, isoflurane was decreased by 0.2% every hour. If this resulted in clinical or laboratory deterioration in parameters of ventilation, the weaning attempts were suspended. Every patient was re-assessed every 4–6 h for suitability for weaning from isoflurane. If clinically indicated, continuous albuterol administration was resumed after the discontinuation of isoflurane. Patients were subsequently weaned from mechanical ventilation and extubated based on the assessment of the individual physician taking care of the child.

Statistical analysis of the changes in the arterial pH and $PaCO_2$ after the administration of isoflurane was performed with the Mann–Whitney U test using Minitab® statistical software (Minitab Inc., State College, PA, USA). Approval from the institutional review board for human research was obtained to review the patient records.

Results

A total of 306 children with status asthmaticus were admitted during the study period. Non-invasive ventilation was used on 35 occasions, and 17 children were intubated to provide mechanical ventilation. Isoflurane was administered for refractory status asthmaticus on 11 occasions in 10 children (age range 1–15 years) during the study period. The demographics, parameters of disease severity and the details of management and outcomes of these patients are described in Table 1.

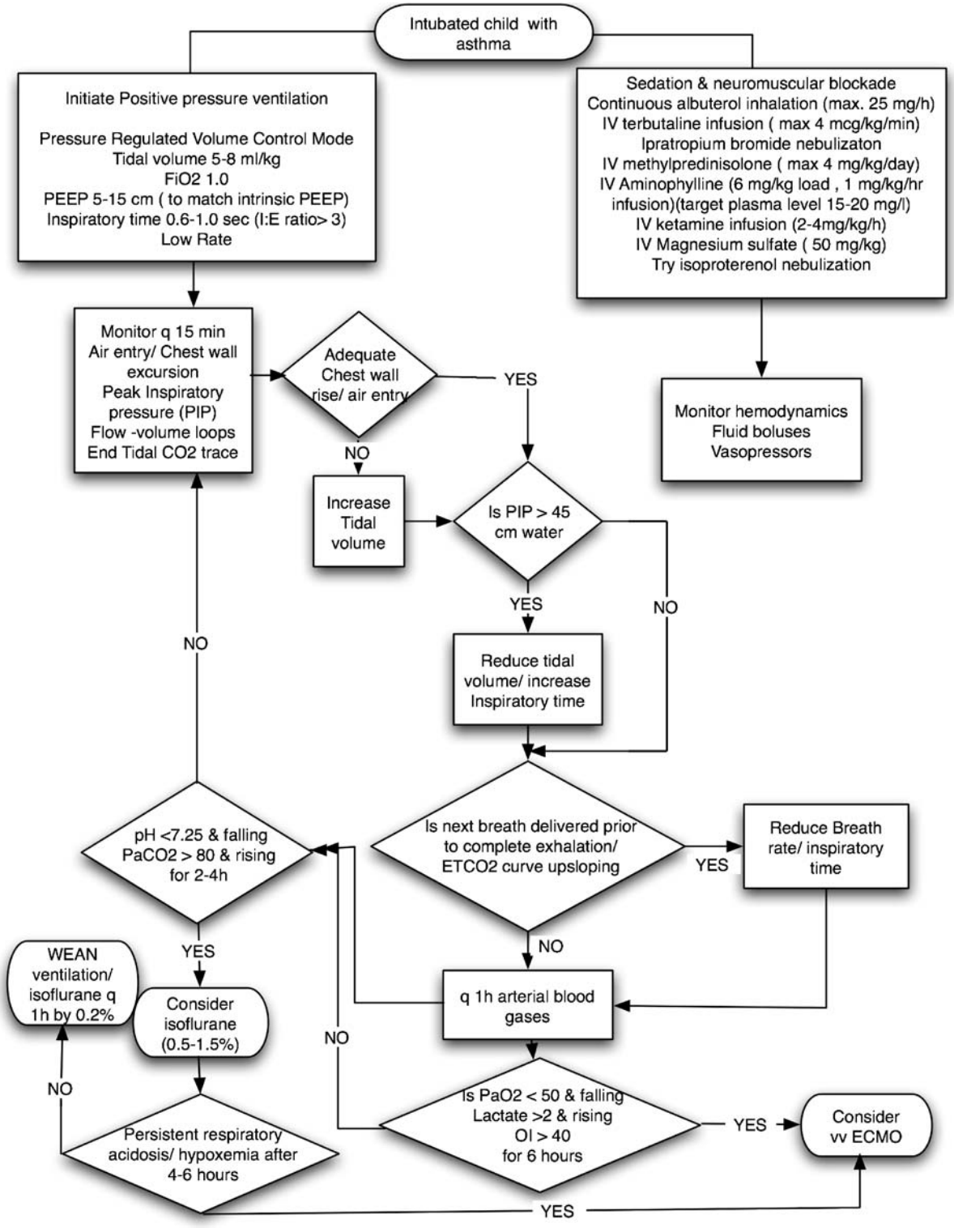
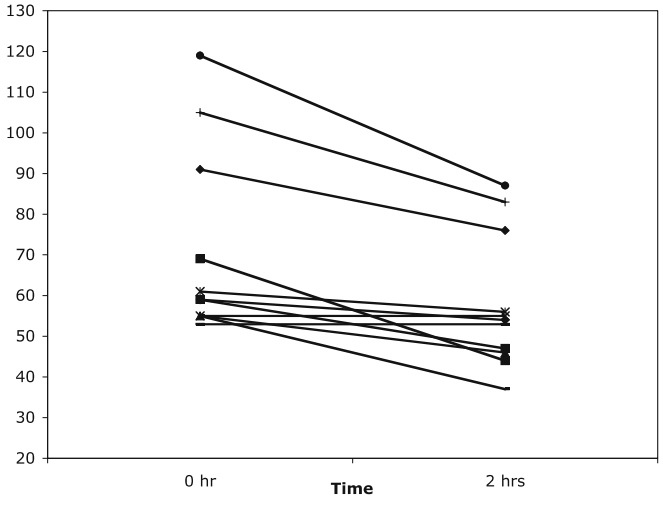
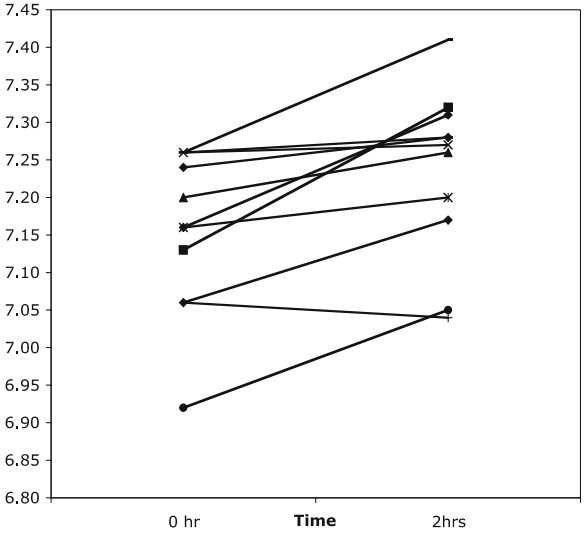


Fig. 1 Management algorithm in children with severe status asthmaticus



	0 h	2 h
Mean	77	58
SD	20	17
p value = 0.032		

Fig. 2 Arterial PCO_2 (in mmHg) before (*0 h*) and 2 h after (*2 h*) initiation of isoflurane



	0 h	2 h
Mean	7.16	7.24
SD	0.11	0.11
p value= 0.028		

Fig. 3 Arterial pH before (*0 h*) and 2 hours after (*2 h*) initiation of isoflurane

Eight children had a prior history of acute asthma exacerbation requiring either hospitalization or ICU admission. In 10 instances the tracheal intubation was performed at the initial scene or by the emergency room staff in the emergency room. One child required tracheal intubation in the pediatric ICU due to continued clinical deterioration. At our institution, cuffed endotracheal tubes are utilized in all children with asthma requiring mechanical ventilation.

Isoflurane was initiated after a median period of 5 h of mechanical ventilation (range 2–8 h). Isoflurane resulted in immediate clinical improvement in all the 11 subjects. In 10 patients progressively improving blood gas values confirmed a sustained improvement in effective alveolar minute ventilation. However, in one patient the response to isoflurane was transient. This child required veno-venous extracorporeal membrane oxygenation (vvECMO) due to continued worsening of respiratory acidosis despite isoflurane therapy. This child was successfully weaned off vvECMO and decannulated after 36 h and made an uneventful recovery.

The arterial PCO_2 and pH values at baseline and after 2 h of isoflurane of all the patients are shown in Figs. 2 and 3 respectively. There was a statistically significant fall in arterial PCO_2 and a significant improvement in pH at 2 h after the initiation of isoflurane ($p = 0.032$ and $p = 0.0284$ respectively).

Isoflurane was administered for a median duration of 35 h. The median total isoflurane dose was 14 MAC h. [MAC (minimum alveolar concentration) is defined as the % inhalational agent required to stop 50% of people moving to a surgical stimulus, in the absence of nitrous oxide (a carrier gas) and an opioid premed. Dose in MAC hours was obtained by multiplying the isoflurane dose in MAC units by the number of hours of administration at that dose. MAC for isoflurane is 1.2%]. The peak concentration of isoflurane administered ranged from 0.5% to 1.5% (0.4–1.25 MAC).

Eight patients required vasoactive support to maintain adequate perfusion pressure. Seven of these patients were on no vasoactive agents prior to the isoflurane. All eight patients were administered dopamine in the dose range of 5–15 μg/kg/min. The administered dose of dopamine was often increased with any increase in the isoflurane dose. In addition, one child also received norepinephrine at 0.2 μg/kg/min.

Nine patients survived and were discharged from the hospital. One child, a 16-year-old girl, died due to severe brain swelling that progressed to brain death. This was most likely secondary to the anoxic brain injury sustained during the cardio-pulmonary arrest at home. She had been dyspneic for approximately 10 h and was taking frequent inhalational bronchodilators at home prior to her cardio-respiratory arrest.

There was no evidence of any renal or hepatic dysfunction in any of the patients.

One child had signs of encephalopathy and tremors. This child was also on high doses of opiates for a prolonged period. These clinical manifestations were con-

Table 1 Patient Characteristics and Outcome

Patient No.	Age / Sex	Duration of acute symptoms (hrs.)	Asthma drugs used	Initial pH	Initial $PaCO_2$	Indication for mechanical ventilation / intubation	Duration of mechanical ventilation	pH at isoflurane initiation	$PaCO_2$ at isoflurane initiation	PaO_2 at isoflurane initiation on F_iO_2 1.0	Peak isoflurane concentration (%)	Isoflurane MAC hrs.	Inotropes	Complications	Outcome
1	8 / M	6	Al, T, I, Mg, Ip, M, K	7.24	59	Hypoxemia	336	7.24	59	41	1.2	170	DA	Air leaks, encephalopathy tremors, abstinence syndrome	Survived
2	6 / M	24	Al, T, I, Mg, Ip, Th, M, K	7.05	88	Respiratory acidosis	96	7.16	69	92	1.3	32	DA	Pneumonia	Survived
3	3 / M	20	Al, T, I, Mg, Ip, M	7.19	55	Hypoxemia	8	7.2	58	84	1	3	–	–	Survived
4	15 / F	24	Al, T, I, Mg, E, Ip, M	7.23	55	Hypercapnia w/ CNS change	18	7.26	78	135	0.5	4	–	–	Survived
5	10 / M	24	Al, T, I, E, Mg, M	6.91	32	Hypercapnia, Respiratory acidosis	32	7.16	61	88	0.8	11	DA	–	Survived
6	16 / F	8	Al, T, Ip, M	6.77	49	Cardio-respiratory	49	6.92	117	72	0.9	9	DA, NE	Anoxic brain damage	Died
7	10 / M	24	Al, T, Mg, I, M, K	7.06	51	Hypoxemia, respiratory fatigue	51	7.06	105	77	0.9	23	DA, E	–	Survived
8	2 / F	96	Al, T, I, Ip, Mg, M	7.26	170	Hypoxemia, respiratory fatigue	170	7.26	82	78	0.6	4	DA	Air leaks, aspiration pneumonia	Survived
9	2 / M	12	Al, T, M	7.02	220	Hypercapnia, Respiratory acidosis	220	7.26	68	88	1.5	14	DA	Persistent Respiratory acidosis requiring ECMO	Survived after ECMO
10	14 / F	12	Al, T, M	7.06	168	Hypoxemia	168	7.06	91	84	1	30	–	–	Survived
11	1 / M	12	Al, T, M	7.11	208	Respiratory fatigue, CNS changes	208	7.13	59	90	1.2	68	DA	–	Survived
Median	8	20		7.06	59		96	7.16	77	84	1	14			
SD	5.5	24.92		0.15	71		105	0.11	20	22	0.3	49			

Key: Al – Albuterol, T – Terabutaline, I – Isoproterenol, Mg – Magnesium sulfate, Ip – Ipratropium, M – Methylprednisolone, E – Epinephrine, K – Ketamine, DA – Dopamine, NE – Norepinephrine, DB – Dobutamine, Th – Theophylline

sidered consistent with an opioid withdrawal syndrome. However, the manifestations persisted despite institution of methadone for treatment of opioid withdrawal. He had also received the largest dose (170 MAC h) and duration (13 days) of isoflurane in our series. He eventually recovered after weeks of pharmacological therapy with benzodiazepines and rehabilitation.

Discussion

Despite the advances in the prevention and treatment of asthma, asthma-related mortality has not declined [1, 2]. Severe exacerbations leading to status asthmaticus remain challenging to manage. Positive pressure mechanical ventilation of these patients is often difficult, leading to dynamic hyperinflation, barotrauma, air leaks and hemodynamic compromise [3, 7, 8]. Children with status asthmaticus who respond poorly to maximal beta-adrenergic and anti-inflammatory therapy are often at risk for these potentially life-threatening complications [14].

Isoflurane, a volatile anesthetic agent, is known to produce bronchodilatation, although the exact mechanism of its effect is not clearly established [9, 10, 12, 15]. Some of the proposed mechanisms include stimulation of beta-adrenergic receptors, direct relaxation of bronchial smooth muscles, antagonism of actions of histamine and acetylcholine and interference with hypercapneic bronchoconstriction [16, 17, 18]. Consequently, isoflurane may produce additional bronchodilatation after a maximal therapy with standard bronchodilators [18, 19]. This bronchodilatory effect is usually immediate and often sustained [19].

Isoflurane is less fat-soluble than other volatile anesthetic agents, and therefore the depth of anesthesia can be rapidly adjusted. It is less arrhythmogenic than halothane, especially in the presence of other adrenergic stimulants as is the case in children with severe status asthmaticus. Recently, newer agents like sevoflurane have been shown to be even more effective bronchodilators than isoflurane [18]. However, at the time of this study, ICU ventilators capable of administering sevoflurane were not commercially available.

There have been a few case reports of use of isoflurane for status asthmaticus in children [12, 15, 19, 20, 21]. Our case series describes one of the largest published reports of use of isoflurane in children with severe life threatening refractory status asthmaticus. Children with asthma requiring mechanical ventilation at our institution are treated using commonly accepted clinical practice guidelines as depicted in the institutional management algorithm in Fig. 1.

Isoflurane is considered for children with severe asthma receiving mechanical ventilation that respond poorly to bronchodilators and anti-inflammatory agents. Extremely high peak inspiratory pressures, evidence of continued air leaks, progressive hypercapneic respiratory acidosis and persistent hypoxemia are considered as indications for isoflurane therapy. Persistent severe hypoxemia (oxygenation index of > 40 or $PaO_2 < 50$ and arterial lactate > 2 mmol/l) at or worsening respiratory acidosis ($pH < 7.2$ and $PaCO_2 > 80$) despite 4–6 h of maximal therapy including isoflurane is often considered as an indication for veno-venous extracorporeal oxygenation.

All of the children in our series exhibited a prompt improvement in alveolar minute ventilation, reflected by improved aeration on auscultation, decreased peak pressures and shortened expiratory phase. They also showed an improvement in arterial $PaCO_2$ ($p = 0.032$) and arterial pH ($p = 0.028$) at 2 h after starting isoflurane. No modifications in tidal volume or rate accompanied the institution of isoflurane. In addition, the median duration of mechanical ventilation and maximal bronchodilator therapy was 5 h prior to the institution of isoflurane. Consequently, the observed improvement in minute ventilation and the blood gas values was most likely due to the bronchodilating effects of isoflurane. There is also a possibility that isoflurane acutely helps "break" an episode of severe bronchospasm, resulting in improved delivery of inhaled bronchodilators.

On 10 occasions, the effect was sustained, leading to continued improvement in minute ventilation. However, in one child, the initial improvement was followed by continued deterioration in respiratory acidosis. This child was placed on vvECMO for extracorporeal CO_2 removal and enabling lung-protective ventilator settings. This child survived without any central nervous system or pulmonary sequelae. This child had extremely high $PaCO_2$ and despite all interventions there was minimal air entry. It is possible that such severe bronchospasm led to very minimal delivery of inhaled isoflurane to airways, resulting in a poor response.

Hypotension was a commonly observed side effect in our patients, resulting in a large proportion of the children requiring inotropic agents or vasopressors. Hypotension is due to the direct vasodilatation and myocardial depression produced by isoflurane in a dose dependent fashion [9, 12, 22]. In all of our patients, the perfusion of organs was well maintained and there was no evidence of any end-organ dysfunction. Although a transient decrease in urinary output was commonly observed, it did not lead to any elevation in blood urea nitrogen or serum creatinine. No child showed any elevation of hepatic transaminases. One child who was exposed to isoflurane on more than one occasion also showed normal hepatic function. These observations are consistent with the previous reports [12, 21].We did not monitor serum fluoride levels in our patients. The previous reports failed to show any fluoride toxicity despite prolonged isoflurane administration [12, 13, 23].

The child who had received the longest duration and the largest cumulative dose of isoflurane (170 MAC h) developed signs of encephalopathy with acute confusional state. He also developed extensive tremors that responded to haloperidol. This child was on prolonged infusions of midazolam and fentanyl. Although opioid withdrawal may

have contributed to his clinical syndrome, we believe that his clinical state was a result of the prolonged exposure to isoflurane. Computerized tomography of the brain did not reveal any abnormalities. Three months later this child had returned to his baseline state without any evidence of neurological sequelae. Similar neurological side effects due to prolonged isoflurane administration have been previously described [20, 24].

In summary, isoflurane produces immediate and often sustained improvement in the alveolar minute ventilation of children with severe life-threatening status asthmaticus who are resistant to conventional treatment including mechanical ventilation. It reduces the peak airway pressure, improves alveolar minute ventilation, and decreases $PaCO_2$. This in turn reduces the risk of barotrauma, pulmonary air leaks, dynamic hyperinflation and cardiovascular compromise. Isoflurane can be safely and effectively administered in the pediatric ICU using a modified ICU ventilator. The pediatric ICU team of physicians, nurses and respiratory therapists can be easily trained on the safe use of this therapeutic modality with the help of the anesthesiology team. In our experience, this therapy decreases the need for extracorporeal support in a large number of patients where all the other therapies have failed. There appear to be no long-term side effects. Isoflurane should be considered in all children with severe acute exacerbation of asthma requiring mechanical ventilation, especially those who fail to respond to a conventional bronchodilator therapy. Further studies are needed to evaluate the newer volatile anesthetics like sevoflurane for use in severe status asthmaticus.

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