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Controversies in the Care of the Acute Asthmatic in the Prehospital and Emergency Department Environments

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Abstract Asthma is an episodic disease of the airways characterized by inflammation and constriction of the bronchi. It has a significant societal impact with over 25 million persons affected in the United States alone and annually accounts for approximately 3300 deaths in the US. Standard therapy for acute severe asthma is effective for most patients, but controversies exist surrounding the care of the impending or actual respiratory failure patient. Non-invasive positive pressure ventilation has been effective in multiple case reports, but lacks large trial evidence to support its use. Intravenous ketamine similarly has supporting case reports, but an absence of rigorous evidence. Finally, parenteral beta-adrenergic medications have a long history of use, but have not been consistently shown to be superior to inhaled short-acting beta agonists. Further, they have been associated with higher rates of adverse effects.

Keywords Asthma · Non-invasive ventilation · Ketamine · Epinephrine · Prehospital · Emergency department

Introduction

Asthma is an episodic disease of the airways consisting of both inflammation and constriction of the airways [1, 2]. The condition was described as synonymous with dyspnea by the ancient physicians Hippocrates and Galen [3]. The definition was narrowed to one close to our modern understanding by Dr. Thomas Wills in his 1675 text *Rational Pharmaceutic* [3]. Asthma is characterized by dyspnea, wheezing, and hyper-responsiveness of the airways [1].

Asthma has a significant societal impact. There has been a rising prevalence in the United States of approximately 2.9–3.8 % per year [4, 5]. In 2010, there were 25.7 million persons in the United States with asthma, of which 7 million were children [5]. Children with active asthma miss 10.5 million school days and adults miss 14.2 work days per year [4]. Patients with asthma exacerbations accounted for 2.1 million emergency department (ED) visits per year in 2009, with 8.4 visits per 100 persons with asthma per year [5]. These visits led to 479,300 hospital admissions in 2009, a rate of approximately 2 admissions per 100 persons per year [5]. The mortality associated with asthma remains at greater 3300 persons per year [4, 5].

The first point of contact for many asthmatic patients is the emergency medical services (EMS) system. Many of the standard ED therapies have moved to the field, allowing earlier intervention for prehospital patients. Therapy for acute exacerbations of asthma presenting to emergency medical services (EMS) or the ED has many generally accepted recommended components. These include inhaled short-acting beta agonists (SABA), systemic corticosteroids, inhaled anticholinergics, and, for severe exacerbations, parenteral magnesium sulfate [6, 7].

The management of patients with impending or actual respiratory failure holds areas where the consensus is less clear and the treatments are more controversial [6]. These patients with acute severe asthma (ASA) are the patients who contribute to the mortality statistics cited above. Our goal will be to discuss three of these controversial

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therapies: non-invasive positive pressure ventilation (NIPPV), parenteral ketamine, and parenteral beta-adrenergic agonists. We will discuss the evidence for and against their use in the prehospital and emergency department environments.

Non-invasive Positive Pressure Ventilation

Traditional management of asthmatics with respiratory failure has included intubation and invasive mechanical ventilation (IMV) [8–12]. This intervention carries with its significant risk. Complications of IMV in the severe asthmatic patient are numerous and include barotrauma, ventilator-associated pneumonia, worsened bronchospasm, hemodynamic collapse, and death [8–12]. Mortality rates asthmatic for patients undergoing IMV range in the literature from 4 to 21 % [10, 13, 14]. Older literature suggests mortality rates as high as 38 % [15]. In one study by Krishnan in 2006, the mortality rate for non-intubated patients was 0.2 % with an IMV mortality rate of 6.9 % [10]. Whether we view intubation and IMV as a marker for the higher risk patients or we attach a degree of causality to IMV, it is clear that efforts should be made to avoid its use in severe asthma patients.

NIPPV has been well established as way of managing impending or actual respiratory failure in patients with chronic obstructive pulmonary disease (COPD) [16–18] and congestive heart failure (CHF) [16, 19]. NIPPV may be administered in the form of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BPAP). The use of NIPPV has been proposed for acute respiratory failure due to asthma exacerbations as well.

Data on NIPPV in asthma are sparse, but growing. A 2012 review by the cochrane collaboration found 6 trials which met their inclusion criteria and they conclude that the "paucity of data" precludes a clear recommendation for or against the therapy [20]. Two other reviews published in 2014 arrived at the same conclusion; there remain a lack of conclusive evidence [21, 22].

Several proposed benefits of NIPPV use in acute asthma have been cited. These include a direct bronchodilatory effect from CPAP [23, 24] as well as an enhancement of the effect of inhaled SABA [23, 24]. NIPPV has also been shown to reduce the work of breathing in the acute severe asthma patient [25, 26].

Hesitancy to employ NIPPV in the acute asthmatic patient relates to concerns that it may worsen some physiologic aspects. Inadequate delivered pressures by face mask were suggested by one paper [8]. The same authors raised concerns about the presence of the face mask impeding immediate access to the airway in the case of "extremely labile patients." [8] Others have raised the concern of increased retained lung volumes leading to an increased intrathoracic pressure, decreased venous return, and circulatory collapse as is seen in IMV [22].

A 2010 retrospective cohort study by Murase et al. looked at NIPPV in adults younger than 80 years with an asthma attack of greater than 7 days duration. Before the introduction of NIPPV at their facility, there were 50 identified presentations of ASA, in which there were nine intubations. After the implementation of NIPPV, the cohort included 57 events. Only two of these patients required intubation, an IMV rate of 18 versus 2 % with NIPPV ($p = 0.01$). This study also demonstrated a decrease in hospital length of stay using NIPPV (10.8 vs. 4.1 days, $p < 0.01$) [27].

In 2012, Hussein published a prospective evaluation of NIPPV in patients who failed conventional therapy with SABA and corticosteroids. Thirty patients were evaluated as to whether they achieved the primary outcome of the absence of acidosis and hypoxia, decrease of at least 20 % in respiratory rate and normal mental status. Twenty-three of the 30 patients (76.6 %) achieved the primary outcome and they concluded that NIPPV can improve respiratory distress and gas exchange in patients failing standard therapy [28].

A 2014 case report by Cappello describes a 35-year-old male who presented in extremis from an asthma attack with hypoxia and severe respiratory acidosis. He received NIPPV supported by benzodiazepine in small doses to aid in his anxiety about the NIPPV mask. He cleared his $PaCO_2$ from 126 mmHg at presentation to 63 mmHg after 90 min and was able to be removed from NIPPV after 4 h [29]. This case demonstrates that judicious use of sedatives can facilitate NIPPV and mediate the panic associated with the face mask in some patients.

A 2015 paper by Pallin et al. investigated the safety of NIPPV in ASA in a retrospective case control study. They reported that 30 patients received NIPPV and 17 were treated with IMV. None of the NIPPV group progressed to IMV and there were no deaths in the NIPPV group or in the control group of matched asthmatic admissions not requiring ventilator support. Hospital length of stay was similar in the NIPPV and IMV groups and longer than the control group. Intensive care unit (ICU) length of stay was 33.4 h for the NIPPV group versus 101.8 h for the IMV group ($p < 0.001$). They conclude that NIPPV is safe and effective in ASA [30••].

A recently published review of the Portuguese National Hospitalization Database demonstrated that NIPPV use for ASA has grown significantly in that country since 2000. In 2000, only 1 % of patients received NIPPV, and in 2010 that number approached 4 %. The data further demonstrate a decrease in mortality versus IMV. They do not show a change in hospital length of stay [31].

All of the studies reviewed are of small size, and most are retrospective in design. The evidence seems encouraging thus far. There is a clear need for larger prospective randomized trials to clearly prove the benefit of this therapy.

Prehospital Use

There have been no studies evaluating NIPPV in the prehospital arena for asthma specifically. NIPPV is available to many EMS systems in the form of CPAP. Some systems have the ability to provide BPAP using transport ventilators [32]. Some of the prehospital datasets reviewing NIPPV in acute respiratory distress include patients whose ultimate diagnosis was asthma [33–35]. These studies demonstrate overall improvement in patients receiving NIPPV in the field with reductions in both rate of IMV and mortality [33–35].

These data support the use of NIPPV in the undifferentiated severe respiratory distress patient, but cannot be used to support recommendations specific to ASA. As with ED use, the data are encouraging, but more studies are needed to reach a definite conclusion.

Ketamine

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor agonist and phencyclidine derivative first approved for clinical use in 1970 [36, 37]. Administered in doses of 1–2 mg/kg intravenously (IV) or 3–5 mg/kg intramuscularly (IM), it produces a dissociative state which leaves intact the airway-protective reflexes of coughing, sneezing, and swallowing [36, 37]. Additionally, it has been shown to maintain respiratory function including tidal volume, functional residual capacity, and minute volume [36–38].

Interest has grown in recent years as to ketamine's utility in the management of asthma that it has a bronchodilatory effect [36, 37]. Ketamine inhibits cerebral uptake of catecholamines and thereby increases their circulating volume and consequently their effect on the airway smooth muscle. It is also a vagal inhibitor, relaxing bronchiolar smooth muscle through anticholinergic effects [36]. It has also been suggested that ketamine has an inhibitory effect on calcium channels which may also aid in smooth muscle relaxation [37]. Because of these effects, ketamine has been recommended by many authors as an induction agent for intubation in ASA [9, 36, 37, 39].

In addition to its use as an induction agent, ketamine has been studied as a direct treatment for ASA. It has been used as an adjunct to IMV, as a direct bronchodilatory agent, as an adjunct to NIPPV, and in effort to avoid NIPPV/IMV.

In the intensive care unit, it has been shown to improve pulmonary function in IMV patients. In 1995, Youssef-Ahmed, et al. published a series of 17 pediatric patients over a 3-year period. Patients received IV boluses of 2 mg/kg followed by maintenance infusions of 20–60 μg/kg/min (1.2–3.6 mg/kg/h). There was an overall increase in the PaO_2/FIO_2 ratio from 116 before ketamine to 248 after 24 h of ketamine ($p < 0.01$). Patients also exhibited a decrease in $PaCO_2$ from 59.8 to 38.7 over the same time period ($p < 0.01$) [40].

A series of 11 adults published by Heshmati in 2003 showed similar results. In this group, the patients were given 1 mg/kg IV boluses followed by 2 h infusions of 1 mg/kg/h. Peak airway pressures were measured with a reduction of the mean from 75.36 ± 4.05 to 39.64 ± 4.59 cm H_2O ($p < 0.005$). Oxygenation values were not reported in the form of PaO_2/FIO_2 ratios, but the PaO_2 values improved from 63 to 92 mmHg ($p < 0.05$). Ventilation also demonstrated significant improvement with a $PaCO_2$ reduction from 71 to 45 mmHg ($p < 0.05$) [41].

Other investigators have evaluated ketamine as a direct bronchodilator in sub-dissociative doses. A randomized, double-blinded, placebo-controlled trial published by Howton in 1996 evaluated 44 adult patients with severe asthma. The participants were randomized either to placebo or to ketamine IV at 0.2 mg/kg followed by an infusion of 0.5 mg/kg/h for 3 h. The study protocol was altered after 9 patients because half of those randomized to ketamine became dysphoric. Subsequently, the initial bolus was reduced to 0.1 mg/kg with the infusion dose unchanged. Both groups demonstrated improvement in their respiratory function as measured by peak flow, respiratory rate, and forced expired volume in one second (FEV_1), but no difference was detected between the groups. There was a slight improvement in patient satisfaction with treatment on a five-point scale (4.3 ± 0.6 vs. 3.7 ± 1.2, $p = 0.0285$) [42].

Another evaluation of sub-dissociative dosing was published in 2005. Here Allen and Macias reported a randomized, double-blinded, placebo-controlled trial of 68 pediatric patients aged 2–18. The dosing was similar to the Howton study, with initial boluses of 0.2 mg/kg and infusions of 0.5 mg/kg/h for 2 h. This study also failed to show improvement in patient condition as measured by pulmonary index scores. There were no adverse effects serious enough to stop the infusion and none were reported at a 48-h follow up [43].

The above noted studies are the only ones of their quality found. The cochrane collaboration review of ketamine for children with ASA in 2012 found only the Allen trial. With the evidence as published, use of sub-dissociative ketamine in non-intubated patients with ASA is not recommended.

The evidence in patients undergoing IMV suggests significant effects at dissociative doses [40, 41, 44]. The question remains, however, whether the desired clinical benefit is available to non-intubated patients at higher doses. Case reports only are available to evaluate this question. In 1992, Sarma reported 2 cases of adults with ASA. Each was approaching respiratory failure and was exhibiting hypoxia. They were given ketamine IV at 0.75 mg/kg bolus dose with 0.15 mg/kg/h infusions. Both patients improved, demonstrating normalization of blood gas analysis. There were some adverse effects in the first patient who described hallucinations. The second patient had a recrudescence of symptoms when the infusion was stopped and rapidly worsened, progressing to intubation and IMV [45].

A 2006 report by Denmark et al. describes two children with ASA failing maximal therapy. Ketamine at a dissociating dose of 2 mg/kg IV was administered, followed by a 2 mg/kg/h infusion. Both children improved with markedly decreased work of breathing and respiratory rate. Both children worsened again after several hours and the infusions were increased to 3 mg/kg/h. Neither child progressed to intubation. Some intermittent confusion was described, but neither child developed complete dissociation. The authors comment that it is not clear why neither child exhibited complete dissociation at these doses [46].

Shlamovitz and Hawthorne report a case of avoided intubation/IMV after administration of ketamine. Their 2011 paper describes a 28-year-old woman with ASA with initial oxygen saturation of 75 % who failed maximal therapy. The decision had been made to intubate. In an effort to avoid IMV, she was given IV ketamine with the dosing regimen described by Sarma, 0.75 mg/kg IV followed by an infusion of 0.15 mg/kg/h. This patient did experience dissociation, but awoke while the infusion was still running. She reported improvement. She was admitted to the intensive care unit and never required intubation [47].

A final case report, still in press at this writing, describes a 36-year-old man with ASA in severe distress hypoxic and bradypneic. The care givers attempted NIPPV, but the patient would not tolerate the mask. He was given 50 mg IV ketamine and he dissociated, allowing the application of NIPPV. He was maintained on continuous SABA through the NIPPV and received additional boluses of ketamine at the same 50 mg dose to a total of 300 mg over 40 min. After that time, he tolerated the NIPPV. After 2 h in the ED, his pH improved from an initial 7.08 to 7.35 and his $PaCO_2$ from 67 to 45 mmHg. He never required intubation and was discharged home in 48 h [48•].

The case reports described suggest that some have had success with ketamine at dissociative doses in the management of ASA. The lack of clinical trials at this dose range hinders our ability to draw conclusions. More research is needed. A review of Clinicaltrials.gov at the time of this writing failed to find any open studies evaluating ketamine in this role. The case reports suggest promise, but recommendations must await further evidence.

Prehospital Use

Evidence for prehospital administration of ketamine in ASA is extremely limited. There are studies documenting ketamine's successful and safe use in the prehospital arena for multiple indications from analgesia, to sedation for excited delirium, to the most common use, sedation for endotracheal intubation [49–52]. One case report described delayed recurrent laryngospasm onset after arrival at the hospital in a patient who had received 500 mg (5 mg/kg) intramuscularly (IM) for excited delirium [53].

The lack of evidence for this indication, despite its reported safety for other indications prevents the recommendation to add this therapy to prehospital ASA management.

Parenteral Beta-Adrenergics

Prior to the advent of SABA medications, the mainstay of ASA management was parenteral epinephrine [54–56]. Other parenteral beta-adrenergics have been used as well, including terbutaline and albuterol [55]. Once SABA became widely available, the use of parenteral adrenergics fell off considerably. Despite this practice change, some authors continue to recommend its use [57–59].

Multiple comparisons of epinephrine or other beta-adrenergics versus inhaled SABA have been published over the years. In 1983, Becker reported a study of 40 children given either subcutaneous (SC) epinephrine or inhaled salbutamol (albuterol). No significant differences were found in pulmonary function testing. They did, however, find an increase in adverse effects including nausea and vomiting, headache, tremor, and palpitations [60]. A 1984 study of 46 children comparing the same therapies found a statistically significant difference in the percentage change of peak expiratory flow rate (PEFR), favoring the SABA [61].

Multiple other papers published in the 1980s and beyond examined the same comparison. Results consistently demonstrated a lack of benefit of parenteral medications over inhaled SABAs in pulmonary function testing [62–66]. One study, by Ruddy et al. from 1986, demonstrated a statistically significant improvement in the Wood-Downes clinical asthma score [67] at 2 h and at discharge in the group treated with SABA (metaproterenol) [65].

One report demonstrated improvement in FEV_1 and PEFR with epinephrine. This was published in 1988 and was conducted as a double-blind randomized, placebo-controlled crossover trial. The authors demonstrated significant improvement in the epinephrine group over the SABA group (metaproterenol) in both the initial and the crossover phases. The authors also report markedly increased side effects of tremor and palpitations [68].

Adverse side effects are common in the studies evaluating epinephrine [60, 61, 63]. A 1988 study of 95 patients who received epinephrine for ASA showed no clinically important arrhythmias in the over 40 age group and 2 episodes of accelerated idioventricular rhythm in the younger group. The authors concluded that epinephrine was safe for use in all age groups [69].

The addition of IV beta-adrenergics has been studied as well. Intravenous epinephrine and terbutaline have been proposed as rescue therapy for life-threatening ASA with the suggested benefit of being titratable to the patient's response and quickly removable in the event of serious adverse side effects manifest [70, 71]. A retrospective chart review by Smith et al. published in 2003 examined the charts of 27 patients in the intensive care unit who received IV epinephrine for their ASA. The dosing was extremely varied, with some receiving loading doses of 50 μg and others as much as 1000 mcg IV. Some had infusions and others did not. The infusions ranged from 3 to 20 mcg/min. No patients died and the only arrhythmia noted was sinus tachycardia. The authors conclude that IV epinephrine is safe in ASA. The efficacy, however, was not clear [70].

Another retrospective review of IV epinephrine was published in 2006. This study evaluated the adverse effects of IV epinephrine in 220 asthma patients. In their data, there were no deaths; however, there were two episodes of supraventricular tachycardia (SVT), four episodes of hypotension, and three episodes of myocardial ischemia. Non-serious adverse events were more frequent, including 23 episodes of sinus tachycardia, 30 episodes of hypertension, and 11 cases of local tissue ischemia. The authors conclude that IV epinephrine is associated with a low rate of severe events [71].

Intravenous terbutaline has also been evaluated. Bogie et al. conducted a randomized double-blinded, placebo-controlled trial of 46 pediatric patients with ASA. The primary outcome measure was ICU length of stay. There was a trend toward a shorter length of stay for the terbutaline group, but the difference did not reach statistical significance [72].

A 2002 meta-analysis by Travers et al. reviewed seven studies and found no benefit and doubled the rate of adverse events as compared with SABA [73]. Finally, a 2012 Cochrane review found "very limited evidence" for the addition of IV beta-adrenergics in children, based on a single study. They found no evidence of benefit in adults [74].

Parenteral beta-adrenergics have been demonstrated in multiple trials to have no clear advantage over inhaled SABA. A small number of trials have demonstrated contrary results. While there remain case reports of harm from the adrenergic effect of both inhaled and parenteral agents including myocardial infarction and even Takotsubo cardiomyopathy [75–77], the more rigorous evidence of clinical trials suggests that serious adverse events are rare. Parenteral beta-adrenergics should be reserved only as a last effort to avoid IMV when other therapies have failed. Even then, intravenous routes should be considered only with great caution.

Prehospital Use

Little data exist on the prehospital use of these interventions for ASA. The conclusions drawn above may be easily extrapolated to the prehospital environment as the interventions are available and familiar to the prehospital provider. A 1994 randomized trial by Quadrel et al. randomized prehospital patients to SC epinephrine, metaproterenol via nebulizer, or both. The results failed to demonstrate an advantage of SC epinephrine over metaproterenol alone.

Conclusions

Standard care for the ASA patient manages the vast majority of asthma patients presenting to EMS and to EDs. The few refractory patients are those from whom mortality statistics are drawn. In these patients, we must consider the more controversial therapies discussed herein. NIPPV awaits larger randomized studies to prove its efficacy. However, the case report literature supports its use. Ketamine has been disproven in sub-dissociative doses, but shows great promise in dissociative dosing both as a primary therapy and as an adjunct to NIPPV. Again, more definitive studies are awaited. Finally, parenteral beta-adrenergics have no clear demonstrated benefit over inhaled SABA and seem to have a higher risk of adverse events. They should be reserved for the refractory patient who has failed other therapies, including NIPPV and ketamine.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Tennyson declares that he has no conflicts of interests.

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by the author.

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