

Ketamine in status asthmaticus: A review

Shweta Goyal, Amit Agrawal

Abstract

Background and Aims: Status asthmaticus is a common cause of morbidity and mortality. The addition of ketamine to the standard treatment regimen of severe asthma has shown to improve outcome and alleviate the need for mechanical ventilation. The purpose of this review is to determine the pulmonary effects of ketamine and to determine whether sufficient evidence exists to support its use for refractory status asthmaticus.

Data Source: MEDLINE, EMBASE, Google Scholar, and Cochrane data bases (from their inception to Jan 2012) using key words “ketamine,” “asthma,” “bronchospasm,” “bronchodilator,” and “mechanical ventilation” were searched to identify the reports on the use of ketamine as a bronchodilator in acute severe asthma or status asthmaticus, and manual review of article bibliographies was done. Relevant databases were searched for the ongoing trials on use of ketamine as a bronchodilator. Outcome measures were analyzed using following clinical questions: Indication, dose and duration of ketamine use, main effects on respiratory mechanics, adverse effects, and mortality. **Results:** Twenty reports illustrating the use of ketamine as a bronchodilator were identified. In total, 244 patients aged 5 months to 70 years received ketamine for bronchospasm. Twelve case reports, 3 double-blind randomized placebo-controlled trials, 2 prospective observational studies, 2 clinical evaluation study, and 1 retrospective chart review were retrieved. Most of the studies showed improved outcome with use of ketamine in acute severe asthma unresponsive to conventional treatment. Patients who received ketamine improved clinically, had lower oxygen requirements, and obviated the need for invasive ventilation. Mechanically-ventilated patients for severe bronchospasm showed reduction in peak inspiratory pressures, improved gas exchange, dynamic compliance and minute ventilation, and could be weaned off successfully following introduction of ketamine. **Conclusion:** In various studies, ketamine has been found to be a potential bronchodilator in severe asthma. However, a large prospective clinical trial is warranted before laying down any definitive recommendations on its use in status asthmaticus.

Keywords: Bronchodilator; emergency department, intensive care unit, ketamine, status asthmaticus

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.117048

Quick Response Code:



Introduction

‘Asthma’ is a Greek word, which means ‘breathless’ or ‘to breathe with open mouth.’ As defined by The Global Strategy for Asthma Management and Prevention Guidelines, “asthma is a chronic inflammatory disorder of the airways associated with increased airway hyper-responsiveness, recurrent episodes of wheezing,

breathlessness, chest tightness, and coughing, particularly at night/early morning.”^[1]

Asthma rates are officially low in India, although there are some recent evidences that the true prevalence is higher than previously thought. The total estimated burden of asthma is an overall prevalence of 3% (30 million patients), and among adults over the age of 15, a median prevalence of 2.4%.^[2]

Asthma exacerbations are a frequent cause of morbidity and mortality. It is a dynamic, often life-threatening state, and response to therapy is variable. While majority of

From:
Department of Pediatrics, Chirayu Medical College and Hospital, Bhopal, India

Correspondence:
Dr. Shweta Goyal, Department of Pediatrics, Chirayu Medical College and Hospital, Bhopal-Indore Highway, Near Bairagarh, Bhopal (M.P.) India.
E-mail: dr_shweta07@rediffmail.com

the patients respond promptly to conventional therapies like nebulized albuterol (salbutamol), anti-cholinergics, theophylline, epinephrine and corticosteroids, some patients have worsening respiratory distress requiring invasive ventilation. Various anesthetic agents like ketamine, isoflurane, sevoflurane, and halothane have been found to have bronchodilator properties. Despite of case reports and research work reported at different times, no definite dosages and guidelines advocating the use of these drugs in severe refractory status asthmaticus have been framed. In the present review, we discuss the various effects of ketamine on respiratory mechanics along with its beneficial uses in refractory status asthmaticus and potential adverse effects in context with currently available data.

Patients and Methods

Search strategy

MEDLINE, EMBASE, Google Scholar, and Cochrane data bases (from their inception to Jan 2012) were searched to retrieve scientific reports related with the use of ketamine as a bronchodilator in acute severe asthma or status asthmaticus. The search terms used were "ketamine," "asthma," "bronchospasm," "bronchodilator," and "mechanical ventilation." Manual review of article bibliographies was done to identify the relevant studies. Following databases were searched for the ongoing trials on use of ketamine as a bronchodilator <http://www.ctri.in/>; <http://www.actr.org.au/>; and <http://www.clinicaltrials.gov/>.

Criteria for inclusion of studies

Case reports, case series, clinical studies, retrospective chart reviews, prospective observational studies, and randomized clinical trials were included if they provided sufficient information on use of ketamine as a bronchodilator.

Participants

Both children and adults were included.

Data collection and analysis

The abstracts and full texts of relevant studies were assessed, and reports not fulfilling the objective of review were excluded. The study design, setting, age of patients included, dose of ketamine used, mode of administration (bolus/continuous infusion), duration of administration, response to treatment, and any adverse effects were noted. The vital parameters, blood gases, oxygen saturation, ventilator settings like pressure requirements, dynamic compliance, and FiO₂ were included as markers of improvement.

Results

Twenty articles illustrating the use of ketamine as a bronchodilator in children and adults were identified. In total, 244 patients received ketamine for bronchospasm. The age of patients ranged from 5 months to 70 years. Out of the total articles, 12 were case report, 2 were clinical evaluation studies, 3 randomized control studies, 2 prospective observational studies, and 1 retrospective chart view.

Setting

Ketamine was used as a rescue agent, unresponsive to first-line agents in intensive care unit, in patients with respiratory failure on mechanical ventilation in 13 articles (53 patients). It was used as an anesthetic agent in asthmatic patients intra-operatively in 3 reports (58 patients). Patients coming to emergency department with status asthmaticus were administered ketamine in 3 studies (131 patients) and postoperatively for analgesia and sedation in asthmatics in 1 study (2 patients).

Dose and duration of ketamine

Ketamine was administered in a bolus dose ranging from 0.1 mg/kg to 2 mg/kg. On the basis of initial response, the dose used for continuous infusion ranged from 0.15 mg/kg/hr to 2.5 mg/kg/hr. The duration of infusion ranged from 1 hour to 5 days.

Outcome

In all cases, ketamine was initiated if there was poor response to first-line agents. In 18 articles, there was a favorable response to ketamine. Patients with severe respiratory distress, improved remarkably clinically, had decreased wheezing sounds and improved oxygen saturation and blood gas. Patients who were intubated and mechanically ventilated for progressive respiratory failure showed improved peak inspiratory pressures, dynamic compliance of lungs, gas exchange, and decreased oxygen requirements. In 2 studies, there was insufficient response to ketamine.

Adverse effects

No major adverse effect was reported in any article. Minor adverse effects like dysphoria, hallucinations, increased secretions occurred. Only a few patients developed mild perturbations in heart rate and blood pressure.

Ketamine

Ketamine was originally named 'CI581.' It is a phencyclidine derivative, water-soluble, and is prepared

with the sodium salt of benzethonium chloride as preservative. The ketamine molecule contains an asymmetrical carbon atom with 2 enantiomers. The S (+) isomer is 3 times more potent and longer acting than R (-) isomer.^[3,4] Ketamine contains a chiral center at the C-2 carbon of the cyclohexanone ring so that 2 enantiomers exist, S (+) ketamine and R (-) ketamine. Commercially available racemic ketamine preparations (such as Ketalar) contain equal concentrations of the 2 enantiomers. The dextro-S(-)-isomer of ketamine has approximately 3- to 4-fold the potency of the levo-R(-)- isomer.^[5,6] The S(+)-isomer appears to be cleared more rapidly than the R(-) isomer, resulting in a shorter duration of effect and more rapid recovery.^[7] Equipotent doses of the S(+)-isomer and the racemate appear to have similar effects on physiologic parameters.^[8] There is evidence to suggest that the R(-)-isomer produces a higher rate of emergence reactions and more agitated behavior than the S(+) isomer.^[9]

Pharmacological properties

Ketamine has a high bioavailability following intravenous or intramuscular administration. The onset of action is rapid, and peak plasma concentrations are seen within 60 seconds of administration. The duration of action after a single bolus injection is 10-15 minutes and distribution half-life is 7-11 minutes. It is cleared via hepatic route with a half-life of 2-3 hours.^[3,4]

Mechanism of action of ketamine as a bronchodilator

The major pathophysiology in asthma comprises of airway hyper reactivity, increased vascular permeability, smooth muscle spasm, and release of inflammatory mediators. In many experimental studies, ketamine has been found to alter respiratory mechanics and produce airway relaxation by acting on various receptors and inflammatory cascades, which mediate bronchospasm. Several mechanisms of action have been proposed to explain this effect.^[10-18]

Ketamine as an immunomodulator

It has been demonstrated that the activation of NMDA (N-methyl-D-aspartic acid) receptors in the lung and airway triggers acute lung injury characterized by pulmonary edema and airway constriction. Ketamine blocks NMDA receptor-induced bronchoconstriction.^[10]

It has been demonstrated that increased nitric oxide levels mediate bronchospasm. Ketamine reduces nitric oxide levels by downregulating inducible nitric oxide synthetase enzyme activity. It inhibits overexpression of mRNA and protein of induced nitric oxide synthetase and reduces the production of nitric oxide in pulmonary tissues.^[11]

Release of inflammatory mediators form the central component of inflammatory changes and airway hyper-reactivity in acute asthma. It has been proved that a clinically significant concentration of ketamine can suppress macrophage function, oxidative ability, and inflammatory cytokine production via reduction of mitochondrial membrane potential. Ketamine interferes with the recruitment of macrophages and cytokine production and thus is a potent anti-inflammatory agent useful in acute asthma.^[12] It also reduces Interleukin-4 (IL-4) concentration as shown in rat asthma models.^[13] Ketamine has also been found to reverse histamine-induced bronchoconstriction and enhance adrenaline-induced bronchodilatation.^[14]

Effect of ketamine on catecholamines

One hypothesis is that ketamine increases synaptic catecholamine levels by blocking the re-uptake of norepinephrine into presynaptic sympathetic neurons. These endogenous catecholamines act on β_2 receptors and lead to bronchodilation. It has been shown that increase in free norepinephrine parallels the peak bronchodilatory effect of ketamine, and this effect can be diminished by β -adrenergic blockade.^[15]

Effect of ketamine on airway smooth muscles

Ketamine exerts an anti-cholinergic effect on bronchial smooth muscles by inhibiting vagal outflow.^[16] It decreases calcium influx in smooth muscles by inhibiting L-type calcium channels, and resultant decrease in intracellular calcium relaxes airway smooth muscle.^[17]

Effect of ketamine on vagal nerve

It has been studied that not only inflammatory cells but also neural mechanisms, by which tachykinins are released from vagal afferent C-fiber, contribute to asthma. Ketamine and its isomers have spasmolytic effects on airway smooth muscles precontracted with tachykinins, thus causing airway relaxation.^[18]

These postulated mechanisms collectively indicate that ketamine attenuates many of the central components of inflammatory changes and airway hyper-responsiveness in asthma and can act as a suitable therapeutic intervention in status asthmaticus.

Effects of ketamine in children and adults

Ketamine is a water-soluble drug, which permits intramuscular, intravenous, oral, intranasal, and rectal administration. Biotransformation occurs primarily in liver. However, the most important pathway involves N-demethylation to norketamine by the cytochrome p450

enzyme system. Norketamine is an active metabolite with one-third the anesthetic potency of ketamine.^[19] The disposition of ketamine varies in children and adults. The pharmacokinetics is similar in children, except that absorption following intramuscular injection is more rapid and hepatic conversion to norketamine is more rapid. Hence, higher concentrations of norketamine are measured.^[20]

Because of this, in addition to lower adsorption rates compared to intramuscular injection, oral and rectal administration is characterized by a significant first-pass effect necessitating higher doses.^[21,22] Emergence phenomena appear to occur more frequently in adults (30-50%) than in children (5-15%), in women more than in men, and at higher doses of ketamine.^[9]

Effect of ketamine on respiration

The influence of ketamine on respiration is varied, and available reports are either equivocal or contradictory. In few studies, it has been found that ketamine, in a dose-related manner, causes a shift of the CO₂ dose-response curve to the right but does not change the slope of the curve i.e., ketamine depresses ventilation but does not reduce the respiratory response to rising levels of carbon dioxide.^[23] However, in another study in pediatric age group, it was found that ketamine is a respiratory depressant, particularly after an intravenous bolus dose. It decreases the responsiveness of respiratory center to CO₂.^[24] Other recent studies demonstrated maintenance of functional residual capacity and minute ventilation in adults^[25] and children.^[26]

Evidences of role of ketamine in status asthmaticus

Status asthmaticus is a unique and dynamic condition requiring rapid and aggressive intervention. Asthmatic patients are predisposed for developing acute exacerbations, which may lead to respiratory failure. In acute asthma, pulmonary mechanisms are severely altered, compromising ventilation and perfusion. There is hyperinflation of lungs, which increases the elastic burden of thorax. Oxygenation, continuous nebulization, inhaled anti-cholinergics, corticosteroids, theophylline, terbutaline, epinephrine, and magnesium sulfate should be introduced simultaneously or in a phased manner, depending on the severity of exacerbation. The potential complications and pitfalls associated with each treatment modality should be identified. Decision of invasive ventilation should not be embarked upon because of its associated complications like air-leak syndromes.

Amongst other unconventional agents, bronchodilator properties of ketamine have been studied extensively in

humans as well as in animal models. Few randomized control trials and isolated case reports advocate usage of this drug in severe refractory status asthmaticus unresponsive to standard therapy. The benefits of ketamine in severe status asthmaticus are promising but controversial.

The unidentified role of ketamine as a bronchodilator was first brought to light by Betts and Parkin in 1971.^[27] They described a 5 ¾-year-old child with severe asthma undergoing extensive allergy skin testing. Ketamine was administered as an anesthetic agent 75 mg/kg intramuscularly. Repeat dosages were given as required. They found that audible wheezing resolved significantly. This suggested that ketamine has some bronchodilator property. The successful resolution of wheezing in this child evoked interest in work on use of ketamine in asthmatic patients.

One year later in 1972, Corssen *et al.* used ketamine as an anesthetic in the management of 40 asthmatic surgical patients aged between 5 to 70 years.^[28] Fourteen patients were asymptomatic, and 22 had bronchospasm during induction of anesthesia. Ketamine (1%) was administered intravenously at 1-2 mg/kg for induction, for maintenance; additional doses of 0.5-1 mg/kg were given at 15 to 30 minutes intervals or when body movements indicated that a repeat dose is desired. In 22 patients with bronchospasm prior to anesthesia who received ketamine for induction, active wheezing cleared in 19 (86%). Two patients improved markedly after receiving repeat doses of ketamine. Authors of the study concluded that ketamine not only protected against precipitation of asthma in asymptomatic group but also alleviated bronchospasm in patients with respiratory distress prior to induction of anesthesia. It also ameliorated acute bronchospasm occurring with other anesthetic agents.

Continuous infusion of ketamine in mechanically ventilated children with refractory bronchospasm has been found to have beneficial effects.^[29] Seventeen patients ranging between 5 months to 17 years with severe asthma on mechanical ventilation were administered ketamine. These 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 ($n = 2$). All patients received conventional treatment for more than 24 hours and mechanical ventilation for 1-5 days prior to initiation of ketamine. An intravenous bolus of 2 mg/kg ketamine, followed by a continuous infusion of 20-60 µg/kg/min, was initiated

as an adjunct to conventional management. Mean duration of ketamine infusion was 40 ± 31 hours. The $\text{PaO}_2/\text{FIO}_2$ ratio in all patients ($n = 17$) and the dynamic compliance in the volume-preset mechanically ventilated patients ($n = 12$) were calculated. $\text{PaO}_2/\text{FIO}_2$ ratio and dynamic compliance increased significantly ($P < 0.0001$) after the initiation of the ketamine infusion. All patients were successfully weaned from mechanical ventilation and discharged. It was concluded that ketamine significantly improves gas exchange and dynamic compliance of chest.

The effect of ketamine on bronchospasm during mechanical ventilation was evaluated in a prospective, placebo-controlled, double-blind trial. Fourteen mechanically ventilated patients with bronchospasm were randomly allocated to either ketamine 1 mg/kg or saline placebo group. The ketamine-treated patients showed an improvement by stethoscopic examination, in P_{O_2} and P_{CO_2} , suggesting that ketamine might be useful in treatment of bronchospasm during mechanical ventilation.^[30]

Intravenous ketamine given in a dissociative dose may be an effective measure to avoid mechanical ventilation in patients with severe asthma exacerbation.^[31] Strube and Hallam reported favorable outcome in a 13-year-old girl following use of this drug. The patient had severe respiratory compromise, which improved after ketamine infusion and avoided intubation and mechanical ventilation.^[32]

Ketamine can be used safely for post-operative analgesia in asthmatic patients.^[33] Owing to its safety profile, it can be used as an adjuvant in management of refractory asthma, even in the presence of myocardial injury.^[34] Continuous infusion of this drug produces better sedation, increase in arterial pressure, and diminution of bronchospasm in critically ill patients.^[35]

Reduction in airway resistance following ketamine use is directly proportionate to the pre-existing bronchial obstruction. More severe the obstruction and higher the airway resistance, more pronounced is reduction in resistance.^[36]

Petrillo *et al.*^[37] conducted a prospective observational study to evaluate the effects of adding ketamine to standard emergency department therapy for patients with status asthmaticus. Ten children with severe asthma unresponsive to standard therapy were enrolled. Ketamine was given at a loading dose of 1 mg/kg, followed by continuous infusion of 0.75 mg/kg/hr

for 1 hour. Clinical asthma score (CAS), vital signs, and peak expiratory flow (PEF) were obtained prior to 10 min and 1 hour after beginning ketamine infusion. There was a significant decrease in CAS, respiratory rate, and oxygen requirement. However, PEF did not show significant improvement.

Heshmati *et al.* administered ketamine to 11 patients with status asthmaticus in respiratory failure.^[38] These patients received ketamine at a loading dose of 1 mg/kg intravenously followed by a continuous infusion of 1 mg/kg/hr for 2 hours. Peak airway pressure values were obtained from the panel of ventilator while PaO_2 and PaCO_2 were measured by using ABG analyzer. They found that mean peak airway pressure and PaCO_2 decreased significantly ($P < 0.005$) and PaO_2 increased significantly ($P < 0.005$) after 15 min and 2 hr of ketamine infusion.

Although studies illustrated that above indicates beneficial effects of ketamine in acute exacerbation of asthma, few randomized trials did not support this role of ketamine. Howton *et al.* conducted a prospective, randomized, double-blind, placebo-controlled trial at an urban teaching hospital to evaluate the efficacy of ketamine as a bronchodilator in acute severe asthma.^[39] They included 53 consecutive patients aged between 18-65 years with acute asthma exacerbation and peak expiratory flow (PEF) less than 40% after receiving albuterol nebulization thrice. Oxygen, continuous nebulized albuterol, and methylprednisolone sodium succinate were administered to all the patients. Following this, patients received either ketamine 0.2 mg/kg bolus, followed by a continuous i.v. infusion at 0.5 mg/kg/hr for 3 hours or a placebo bolus and infusion for similar duration. Bolus dose of ketamine was reduced to 0.1 mg/kg after first 9 patients due to occurrence of dysphoric reactions. There was significant improvement in PEF ($F = 3.637$, $P = 0.004$), Borg Score ($F = 22.959$, $P = 0.001$), respiratory rate ($F = 8.11$, $P = 0.0001$), and FEV-1 ($F = 9.076$, $P = 0.001$) in each treatment group. However, there was no significant difference in outcome between both groups. Authors concluded that ketamine has no bronchodilatory effects, although some satisfaction was there after ketamine use.

Allen *et al.* also did not find encouraging results with usage of ketamine.^[40] Continuous infusion of ketamine was administered to pediatric patients presenting with acute asthma. Sixty-eight patients were enrolled, 33 randomized to ketamine infusion and 35 to placebo. Exclusion criteria included temperature greater than 39 degrees C (102 degrees F), focal infiltrate on

radiograph, or any glucocorticoid use in the last 72 hours. Eligible patients received 3 treatments with albuterol, ipratropium bromide, and a dose of oral or parenteral glucocorticoids. Patients were randomized to receive an intravenous bolus of 0.2 mg/kg of ketamine, followed by a 2-hour ketamine infusion at 0.5 mg/kg/hour or an equal-volume regimen with normal-saline placebo. At completion of infusion, there was no significant improvement in pulmonary index score (15 point score). There were no adverse effects. These trials did not substantiate the role of ketamine in asthma, as their subset of patients did not improve significantly.

However, bronchodilatory effects of ketamine cannot be undermined, and results of these studies cannot be extrapolated. Ketamine is being used sporadically in emergency rooms for severe asthma in pediatric as well as adult age group. The results with use of ketamine in severe refractory status asthmaticus have been satisfactory. However, due to the lack of sufficient randomized, case control, blinded studies, its role as a bronchodilator is not established. Other clinical trials and case reports, which evaluated bronchodilator properties of ketamine in pediatric age group and in adults, are illustrated in Table 1 and Table 2, respectively.

Adverse effects

Ketamine is a relatively safe drug owing to its property of preservation of airway reflexes. However, it has been known to increase airway secretions, thus requiring

anti-sialogogues like atropine and glycopyrrolate. Disorientation, sensory and perceptual illusions, and vivid dreams on recovery might occur. Benzodiazepines have proven to be the most effective agents for prevention of these phenomena. Laryngospasm, transient rise in intracranial pressure, increased muscle tone, apnea with high doses or rapid administration, and nystagmus are the other infrequent adverse effects attributed to ketamine.^[3,4]

Conclusion

Ketamine is a versatile and inexpensive drug. Its place in status asthmaticus cannot be overemphasized where most of the patients respond to conventional drugs. It has been empirically used as a bronchodilator in severe status asthmaticus refractory to routine medications and has been found to obviate the need for mechanical ventilation in various studies. The limited magnitude of side effects permits its use in status asthmaticus when all other agents fail. Still, its use in asthma is debatable. There is a dearth of randomized studies to establish its favorable effects in asthmatic patients and paucity of information regarding its optimum dose. Physicians have administered bolus doses ranging from 0.1-2 mg/kg and continuous infusion from 0.15 to 2.5 mg/kg/hr. The few prospective observational studies, which described the use of ketamine in a group of asthmatic patients, had no control groups to further clarify its use. The sample size is small in most of the studies. The dosage and duration

Table 1: Tabular list of case reports and clinical investigations of ketamine use in acute asthma in pediatric age group

Author (s) year	No. of patients	Age	Study design	Dose of ketamine	Duration	Markers of improvement	Results
Betts <i>et al.</i> , 1971 ^[27]	One	5¾-yr	Case report	l/M 75 mg, then 10 mg q15 min	-	Clinical	Improvement
Corssen <i>et al.</i> , 1972 ^[28]	40	5-70 yrs	Case report	1-2 mg/kg bolus, 0.5 mg/kg	Variable	ABG's, Clinical	Improvement
Strube and Hallam, 1986 ^[32]	One	13 yr	Case report	1.4 mg/kg i.v. bolus, 2.5 mg/kg/hr	8 hrs	ABG's, clinical, RR*, mental Status	Improvement
Rock <i>et al.</i> , 1986 ^[41]	Two	4 yr, 10 yr	Case report	0.5 mg/kg i.v. bolus, 1 mg/kg, 1 mg/kg/hr	24 hrs	Improved inspiratory pressure, ABG's, Clinical improvement	Improvement
Youssef-Ahmed <i>et al.</i> , 1996 ^[29]	17	5 mo-17 y	Retrospective chart review	2 mg/kg bolus, 20-60 micr/kg, min	Variable mean 40 Hrs	Ventilatory parameters/gas exchange	Improvement
Nehama <i>et al.</i> , 1996 ^[16]	One	8 mo	Case report	1.4 mg/kg i.v bolus twice, 0.15-0.2 mg/kg/hr	40 hrs	Peak inspiratory pressure, wheezing, chest movement	Improvement
Fisher, 1997 ^[42]	One	5 yr	Case report	200 mg bolus	Bolus only 1 hr	ABG's	Improvement
Petrillo <i>et al.</i> , 2001 ^[37]	10	5-16 yrs	Prospective, observational study	1 mg/kg bolus, 0.75 mg/kg/hr	1 hr	ClinicalAsthma score, vital, PEF, SpO ₂	Improvement
Heshmati <i>et al.</i> , 2003 ^[38]	11	15-40 yrs	Prospective, observational study	1 mg/kg bolus, 1 mg/kg/hr	2 hrs	Peak airway pressure, Pco ₂ , Po ₂	Improvement
Allen <i>et al.</i> , 2005 ^[40]	68	2-18 y	DBRPC	0.2 mg/kg i.v. bous, 0.5 mg/kg/hr for 2 hrs	2 hr	Pulmonary index score	No improvement

*RR: Respiratory rate

Table 2: Tabular list of case reports and clinical investigations of ketamine use in acute asthma in adults

Author (s) year	No.	Age	Study design	Dose of ketamine	Duration	Markers of improvement	Results
Huber <i>et al.</i> , 1972 ^[36]	17	adult	Case report	0.1 mg/lb body wt f/b 0.5 and 1 mg/lb body wt at 5 and 20 min intervals	bolus	Clinical, airway resistance	improved
Park <i>et al.</i> , 1987 ^[35]	One	24 yr	Case report	i.v. 20 mg bolus, i.v. 20-100 mg/hr	5 days	Peak airway pressure, ABG's, PE*	Satisfactory
Turnpenny <i>et al.</i> , 1991 ^[43]	One	35 yr	Case report	Iv bolus	Bolus only	Peak airway pressure, ABG's, PE*	Improvement
Achar <i>et al.</i> , 1993 ^[34]	One	53 yrs	Case report	20 mg bolus, 20-30 mg/hr	18 hrs	Vitals, ABG's	Improvement
Hemming <i>et al.</i> , 1994 ^[44]	One	28 yr	Case report	2.5 mg/kg/hr	26 hrs	Compliance, gas exchange, wheezing, air movement	Improvement
Hemmingsen <i>et al.</i> , 1994 ^[30]	14		DBRPC [†]	i.v. 1 mg/kg	Bolus only	Clinical, ABG's	Improvement
Howton <i>et al.</i> , 1996 ^[39]	53	18-65 yrs	DBRPC [†] trial	0.2 mg/kg bolus, 0.5 mg/kg/hr	3 hrs	Peak flow, borg score, RR [‡] , FEV1	No significant
Reig <i>et al.</i> , 2004 ^[45]	One	47 yrs	Case report	25 mg bolus, 15 mg/hr	80 hrs	Vitals, ABG's, ventilatory parameters	Improvement
Shlamovitz <i>et al.</i> , 2008 ^[31]	One	Adult	Case report	0.75 mg/kg bolus, 0.15 mg/kg/hr	-	Oxygen saturation	Improvement

*Physical examination, [†]Double-blind, randomized, Placebo-controlled trial, [‡]RR: Respiratory rate

of conventional medication have not been mentioned in most of the studies. Reporting bias where negative studies for Ketamine use go unpublished is likely. Keeping these loopholes in mind, it can be concluded that ketamine is a potent bronchodilator to be considered as a rescue therapy in refractory status asthmaticus. However, it warrants further well-designed studies to identify its role in acute asthma.

References

- Global Strategy for Asthma Management and Prevention. Available from: http://www.ginasthma.org/pdf/GINA_Pocket_2010a.pdf. [Last accessed on 2011 Jul 20].
- Aggarwal AN, Chaudhry K, Chhabra SK, D'Souza GA, Gupta D, Jindal SK, *et al.* Prevalence and risk factors for bronchial asthma in Indian adults: A multicentre study. *Indian J Chest Dis Allied Sci* 2006;48:13-22.
- Stevenson C. Ketamine: A review. *Update in Anaesthesia* 2005;20:25-9.
- Reich DL, Silvey G. Ketamine: An update on the first twenty-five years of clinical experience. *Can J Anaesth* 1989;36:186-97.
- Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J. Differential psychopathology and patterns of cerebral glucose utilization produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). *Eur Neuropsychopharmacol* 1997;7:25-38.
- Zeilhofer HU, Swandulla D, Geisslinger G, Brune K. Differential effects of ketamine enantiomer on NMDA receptor currents in cultured neurons. *Eur J Pharmacol* 1992;213:155-58.
- Adams HA, Bauer R, Gebhardt B, Menke W, Baltes- Gotz B. Total IV anesthesia with S-(+)-ketamine in orthopedic geriatric surgery: Endocrine stress reaction, hemodynamics and recovery. *Anaesthesist* 1994;43:92-100.
- Geisslinger G, Hering W, Thomann P, Knoll R, Kamp HD, Brune K. Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. *Br J Anaesth* 1993;70:666-71.
- White PF, Ham J, Way WL, Trevor AJ. Pharmacology of ketamine isomers in surgical patients. *Anesthesiology* 1980;52:231-9.
- Sato T, Hirota K, Matsuki A, Zsigmond EK, Rabito SF. The role of the N-Methyl-D-Aspartic acid receptor in the relaxant effect of ketamine on tracheal smooth muscle. *Anesth Analg* 1998;87:1383-8.
- Zhu MM, Qian YN, Zhu W, Xu YM, Rong HB, Ding ZN, *et al.* Protective effects of ketamine on allergen-induced airway inflammatory injury and high airway reactivity in asthma: Experiment with rats. *Zhonghua Yi Xue Za Zhi* 2007;87:1308-13.
- Chang Y, Chen TL, Sheu JR, Chen RM. Suppressive effects of ketamine on macrophage functions. *Toxicol Appl Pharmacol* 2005;204:27-35.
- Zhu Meihua, Zhu Minmin, Zhou Qinbai, *et al.* Effect of aerosolized ketamine inhalation on IL-4 concentration in asthma rat model. *J Clin Anaesthesiol* 2004-06. Available from: http://en.cnki.com.cn/Article_en/CJFDTOTAL-LCMZ200406017.htm. [Last accessed date 2012 sep].
- Hirota K, Sato T, Rabito SF, Zsigmond EK, Matsuki A. Relaxant effect of ketamine and its isomers on histamine-induced contraction of tracheal smooth muscle. *Br J Anaesth* 1996;76:266-70.
- Mathewson HS, Davis TA. Bronchodilator properties of ketamine. *Respir Care* 1997;42:292-3.
- Nehama J, Pass R, Bechtler-Karsch A, Steinberg C, Notterman DA. Continuous ketamine infusion for the treatment of refractory asthma in a mechanically ventilated infant: Case report and review of the pediatric literature. *Pediatr Emerg Care* 1996;12:294-7.
- Pabeliek CM, Jones KA, Street K, Lorenz RR, Warner DO. Calcium concentration-dependent mechanisms through which ketamine relaxes canine airway smooth muscle. *Anesthesiology* 1997;86:1104-11.
- Hirota K, Sato T, Rabito SF, Zsigmond EK, Matsuki A. Relaxant effect of ketamine and its isomers on histamine-induced contraction of tracheal smooth muscle. *Br J Anaesth* 1996;76:266-70.
- Ebert B, Mikkelsen S, Thorkildsen C, Borghjerg FM. Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *Eur J Pharmacol* 1997;333:99-104.
- Grant IS, Nimmo WS, McNicol LR, Clements JS. Ketamine disposition in children and adults. *Br J Anaesth* 1983;55:1107-11.
- Qureshi FA, Mellis PT, McPadden MA. Efficacy of oral ketamine for providing sedation and analgesia to children requiring laceration repair. *Pediatr Emerg Care* 1995;11:93-7.
- Roelofse JA, Joubert JJ, Swart LC, Stander I, Roelofse PG. An evaluation of the effect of oral ketamine and standard oral premedication in the sedation of paediatric dental patients. *J Dent Assoc S Afr* 1996;51:197-201.
- Bourke DL, Malit LA, Smith TC. Respiratory interactions of ketamine and morphine. *Anesthesiology* 1987;66:153-6.
- Hamza J, Ecoffey C, Gross JB. Ventilatory response to CO2 following intravenous ketamine in children. *Anesthesiology* 1989;70:422-25.
- Mankikian B, Cantineau JP, Sartene R, Clergue F, Viars P. Ventilatory pattern of chest wall mechanics during ketamine anesthesia in humans. *Anesthesiology* 1986;65:492-99.
- Shulman D, Beardsmore CS, Aronson HB, Godfrey S. The effect

- of ketamine on the functional residual capacity in young children. *Anesthesiology* 1985;62:551-56.
27. Betts EK, Parkin CE. Use of ketamine in an asthmatic child. *Anesth Analg* 1971;50:420-1.
 28. Corssen G, Gutierrez J, Reves JG, Huber FC Jr. Ketamine in the anesthetic management of asthmatic patients. *Anesth Analg Curr Res* 1972;51:588-96.
 29. Youssef-Ahmed MZ, Silver P, Nimkoff L, Sagy M. Continuous infusion of ketamine in mechanically ventilated children with refractory bronchospasm. *Intensive Care Med* 1996;22:972-6.
 30. Hemmingsen C, Nielsen PK, Odorico J. Ketamine in the treatment of bronchospasm during mechanical ventilation. *Am J Emerg Med* 1994;12:417-20.
 31. Shlamovitz GZ, Hawthorne T. Intravenous ketamine in a dissociating Dose as a temporizing measure to avoid mechanical ventilation in adult patient with severe asthma exacerbation. *J Emerg Med* 2008;41:492-4.
 32. Strube PJ, Hallam PL. Ketamine by continuous infusion in status asthmaticus. *Anaesthesia* 1986;41:1017-9.
 33. Jahangir SM, Islam F, Chowdhury SN, Aziz L, Ghani MA. Ketamine infusion for postoperative analgesia: A prospective cohort study in asthmatics. *Bangladesh Med Res Coun Bull* 1993;19:21-7.
 34. Achar MN, Achar KN. Efficacy of ketamine infusion in refractory asthma complicated by acute myocardial infarction. *Anaesth Intensive Care* 1993;21:115-7.
 35. Park GR, Manara AR, Mendel L, Bateman PE. Ketamine infusion. Its use as a sedative, inotrope and bronchodilator in a critically ill patient. *Anaesthesia* 1987;42:980-3.
 36. Huber FC Jr, Reves JG, Gutierrez J, Corssen G. Ketamine: Its effect on airway resistance in man. *South Med J* 1972;65:1176-80.
 37. Petrillo TM, Fortenberry JD, Linzer JF, Simon HK. Emergency department use of ketamine in pediatric status asthmaticus. *J Asthma* 2001;38:657-64.
 38. Heshmati F, Zeinali MB, Noroozina H, Abbaivash R, Mahoori A. Use of ketamine in severe status asthmaticus in intensive care unit. *Iran J Allergy Asthma Immunol* 2003;2:175-80.
 39. Howton JC, Rose J, Duffy S, Zoltanski T, Levitt MA. Randomized, double-blind, placebo-controlled trial of intravenous ketamine in acute asthma. *Ann Emerg Med* 1996;27:170-5.
 40. Allen JY, Macias CG. The efficacy of ketamine in pediatric emergency department patients who present with acute severe asthma. *Ann Emerg Med* 2005;4:43-50.
 41. Rock MJ, Reyes de la Rocha S, L'Hommedieu CS, Truemper E. Use of ketamine in asthmatic children to treat respiratory failure refractory to conventional therapy. *Crit Care Med* 1986;14:514-16.
 42. Fisher MM. Ketamine hydrochloride in severe bronchospasm. *Anesthesia* 1977;32:771-2.
 43. Turnpenny PD, Nash SF. Ketamine in severe acute asthma. *Arch Emerg Med* 1991;8:291-2.
 44. Hemming A, MacKenzie I, Finfer S. Response to ketamine in status asthmaticus resistant to maximal medical treatment. *Thorax* 1994;49:90-1.
 45. Galbis-Reig D, Rasansky MA. A case presentation and literature review of successful ketamine administration in a patient with refractory status asthmaticus. *Internet J Intern Med* 2004;5:31.

How to cite this article: Goyal S, Agrawal A. Ketamine in status asthmaticus: A review. *Indian J Crit Care Med* 2013;17:154-61.

Source of Support: Nil, **Conflict of Interest:** None declared.

Author Help: Reference checking facility

The manuscript system (www.journalonweb.com) allows the authors to check and verify the accuracy and style of references. The tool checks the references with PubMed as per a predefined style. Authors are encouraged to use this facility, before submitting articles to the journal.

- The style as well as bibliographic elements should be 100% accurate, to help get the references verified from the system. Even a single spelling error or addition of issue number/month of publication will lead to an error when verifying the reference.
- Example of a correct style
Sheahan P, O'leary G, Lee G, Fitzgibbon J. Cystic cervical metastases: Incidence and diagnosis using fine needle aspiration biopsy. *Otolaryngol Head Neck Surg* 2002;127:294-8.
- Only the references from journals indexed in PubMed will be checked.
- Enter each reference in new line, without a serial number.
- Add up to a maximum of 15 references at a time.
- If the reference is correct for its bibliographic elements and punctuations, it will be shown as CORRECT and a link to the correct article in PubMed will be given.
- If any of the bibliographic elements are missing, incorrect or extra (such as issue number), it will be shown as INCORRECT and link to possible articles in PubMed will be given.