ORIGINAL ARTICLE

Use of Ketamine in Refractory Bronchospasm- A Study of 20 Cases

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Abstract:

Objective: To study the effect of ketamine in patients of severe wheezing due to bronchiolitis who are refractory to the standard treatment. *Methods:* Prospective study including 104 children between 2 months to 2 years who presented to us with severe wheezing due to bronchiolitis. Initially they were treated with humidified oxygen and adrenaline nebulisation. Children with no response after 48 hours were given intravenous ketamine as a bolus in dose of 1 mg/kg. Patients were monitored with Uyan score and oxygen saturation for 1 hour and those without considerable improvement were given continuous infusion at 10 ìgm/kg/min. *Results:* 104 patients were identified with severe wheezing due to bronchiolitis during study period. 84 (81%) patients responded well to standard treatment. 20 (19%) patients who did not improve were treated with ketamine. All patients responded to intravenous ketamine as bolus and showed noticeable improvement in 1 hour with improvement in scoring parameters. 14 (70%) patients had to be given infusion of ketamine and they were gradually weaned off the drip in an average of 15 hours. *Conclusion:* Use of ketamine in patients with severe wheezing due to bronchiolitis who failed to respond to standard treatment showed improvement which obviated the need for intubation and mechanical ventilation.

Key Words: Wheezing, Ketamine.

Introduction:

Infants are more prone to wheeze, owing to different set of lung mechanism as compared to older children and adults. The obstruction to flow is affected by airway caliber and compliance of the infant lung. Wheezing is common in infants and there are no specific guidelines for treatment of such patients [1]. Response to bronchodilators is unpredictable, regardless of cause, but suggests a component of bronchial hyper reactivity. Ketamine, is a Phenacyclidine derivative and an intravenous anesthetic [2]. Ketamine was synthesized in 1962, by Stevens and was first used in humans by Crossen and Dommino, in 1965 [3]. It was released for clinical used in 1970 and is still used in variety of clinical setting [2]. It has also been demonstrated to cause bronchodilation thereby reducing airway resistance and increases lung compliance [4, 5]. Ketamine has been successfully used in management of acute severe asthma in adults and children but rarely used in infants with refractory wheezing due to bronchiolitis [1]. For this reason we designed a prospective observational study in patients presenting to us with refractory wheezing due to bronchiolitis unresponsive to standard treatment.

Material and Methods:

The study was conducted in the pediatric intensive care unit of Krishna Hospital, Karad Maharashtra. The study was conducted between November 2011 and September 2012. Children

aged 2 months to 2 years, presenting with first episode of wheezing with respiratory distress were considered for the study. Chest radiograph was done for all patients which showed bilateral hyperinflation suggestive of bronchiolitis. The children were initially treated with humidified oxygen and nebulisation with adrenaline. This treatment was continued for 48 hours. Our patients were monitored by Uyan score [6] and oxygen saturation (SpO_2) with FiO2 of 0.6. As the patient profile in our hospital comes from low socioeconomic strata we could not use invasive parameters like arterial blood gases for monitoring the patients due to financial constrains.

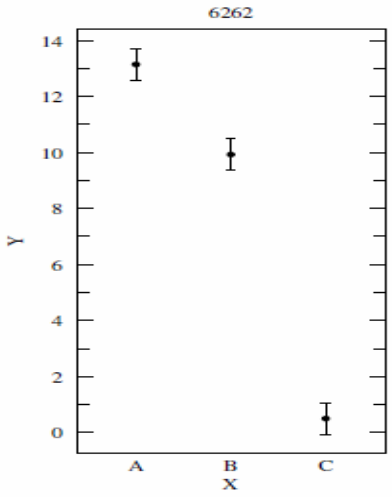
The patients who did not respond to conventional method of treatment as mentioned above were considered for Ketamine use. A Uyan score of 9 was taken as a cut off for use of Ketamine. A total of 20 patients were considered for Ketamine use. An informed parental consent was obtained for the same. Patients with congenital heart disease, central nervous system problems (increased intracranial pressure, intracranial mass lesions), and patients with other contraindications to Ketamine like vascular aneurysms, open eye injury or other ophthalmic disorders, in which a Ketamine induced increase in intraocular pressure would be detrimental hence were excluded. Patients with family or personal history of asthma or atopy were also excluded.

Patients were given intravenous ketamine as 1 mg/kg bolus and improvement in Uyan score and SpO_2 were monitored after 1 hour. Those patients who did not have improvement in Uyan score $\geq$ 9 were considered for infusion. Ketamine was infused at a rate of 10ì/kg/min. Although in this study we did not use control group, the patient's respiratory variables were measured with parameters like Uyan score and SpO_2 prior to and one hour after Ketamine infusion and after weaning off the Ketamine. Data were analyzed using SPSS software and were expressed as mean ± standard deviation (SD) and compared using, unpaired't' test and repeated measure ANOVA test. Comparison was done on the basis of Bonferroni correction and statistical significance was considered at $p < 0.05$.

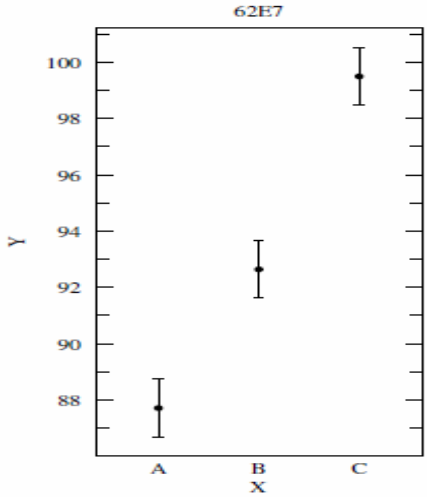
Results:

One hundred four patients presented with severe wheezing with respiratory distress during the study period. Eighty four (81%) patients responded to standard treatment. Twenty (19%) patients were enrolled for Ketamine use who failed to respond with the standard therapy. Six (30%) patients responded to IV Ketamine bolus leaving fourteen (70%) patients for Ketamine infusion. The details of these patients, Uyan score and SpO_2 at three intervals namely prior to Ketamine use (T0), one hour after Ketamine infusion (T1) and at the time when Ketamine was weaned off (TW) are given in Table 1. The mean valves obtained for Uyan score at T0, T1 and TW were 13.14 ± 1.17, 9.82 ± 1.21 and 0.5 ± 0.65 respectively. The mean valves obtained for SpO_2 at T0, T1 and TW were 87.71% ± 2.05%, 92.64% ± 2.46% and 99.5% ± 0.51% respectively. This showed that there were gradual improvements in the Uyan score and progressive rise in the oxygen saturation after Ketamine use (Figures 1A and 1B).

Figure 1A & 1B– Mean and 95% CI of Uyan Score and SpO_2 at A- prior to Ketamine Use B- One Hour after Ketamine Use and C-Weaned off from Ketamine.



Uyan Score



SpO_2

Table 1: Sexwise Distribution of Mean Uyan Score, Mean % Oxygen Saturation & Mean Wean Hrs

Sex	Uyan Score						Oxygen Saturation						Wean hrs	
	T0		T1		TW		T0		T1		TW			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Males	13.11	1.27	10.00	1.22	0.33	0.50	88.44	1.88	92.89	2.89	49.56	46.91	15.78	12.82
Females	13.20	1.10	13.20	1.10	0.80	0.84	86.40	1.82	92.20	1.64	63.40	48.75	14.80	6.87
Unpaired 't' value	0.13	1.34	0.29	1.13	1.32	2.80	1.97	1.07	0.05	3.10	0.52	1.08	0.16	3.48
p - value	0.90	0.82	0.78	0.81	0.21	0.20	0.07	>0.99	0.64	0.29	0.61	0.85	0.88	0.24

Table 2: Agewise Distribution of Mean Uyan Score, Mean % Oxygen Saturation & Mean Wean Hrs

Sr. No	Age in months	No.	Uyan Score						Oxygen Saturation						Wean hrs	
			T0		T1		TW		T0		T1		TW			
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	<6	3	12.67	1.16	10.33	1.53	0.67	1.16	88.67	1.53	92.67	1.16	99.33	0.58	8.67	3.06
2	≥6to12	6	13.17	0.98	9.17	0.41	0.17	0.41	87.00	2.45	93.83	2.93	99.67	0.52	10.67	7.00
3	≥12to24	5	13.40	1.52	10.60	1.34	0.80	0.45	88.00	1.87	91.20	1.92	99.40	0.55	25.20	11.10
Average			13.14	1.17	9.93	1.21	0.5	0.65	87.71	2.05	92.64	2.47	99.5	0.52	15.43	10.77
F			0.33		2.70		1.54		0.70		1.73		0.52		5.46	
p-value			0.72		0.11		0.26		0.52		0.22		0.61		0.023*	

There was no significant difference in two sexes as judged by unpaired 't' test for the mean and SDs of Uyan score , Oxygen Saturation and Weaning time.

When consideration was given to age groups between 2 months to < 6 months, ≥ 6 months to < 12 months & ≥ 12 months, it was observed that there was a significantly lesser weaning time at the earlier ages. With increasing age the weaning time of Ketamine drip also increased. There was no significant difference in the mean Uyan scores and mean oxygen saturation values in different age groups. (Table 2)

Repeated ANOVA test was applied to the data of patients of the two parameters studied namely Uyan score and oxygen saturation which showed an F value of 1096.5 for Uyan score and 167.07 for oxygen saturation. Further, this was supported by Bonferroni correction which was applied to the Uyan score and oxygen saturation readings at three intervals and the statistical differences between the intervals were compared and it was found that both the parameters were statistically significant. (Table 3 and 4) Bonferroni correction was found statistically significant signifying that given result is unlikely to have occurred by chance.

Table 3: ANOVA Test Application on Uyan Score

Groups	Mean difference	F	Bonferroni	p
T0 vs T1	3.214	1096.5	11.454	<0.001
T0 vs TW	12.643		45.051	<0.001
T1vsTW	9.429		33.598	<0.001

Table 4: ANOVA Test Application on Oxygen Saturation

Groups	Mean difference	F	Bonferroni	p
T0 vs T1	-4.929	167.07	7.610	<0.001
T0 vs TW	-11.786		18.198	<0.001
T1vsTW	-6.857		10.588	<0.001

Discussion:

Wheezing in infants and children is common and can be due to bronchiolitis (viral infection), chlamydial infection, congenital airway and heart anomalies, mediastinal masses and foreign body aspiration. There are no specific guidelines for treatment of acutely wheezing infants [1]. Chest radiogram of all our patients revealed bilateral hyperinflation suggestive of bronchiolitis. Thus all patients were treated with standard treatment of humidified oxygen and adrenaline nebulisation. Eighty four (81%) of the 104 patients showed improvement by the standard treatment while 20 patients did not show signs of improvement or detoriated towards respiratory failure. Betts and Parkin in 1971 has first used Ketamine as an anesthetic agent in a 5 years old asthmatic patient which relieved the bronchospasm [7]. In a year's period Corssen (1972) has made a similar observation [4]. With the knowledge of various case reports and randomised control trials related to Ketamine use for acute exacerbation of asthma in pediatric patients as well as adults the decision of using ketamine has been taken.[1,4,7,8,10-12,19-24]

Ketamine has many pharmacological properties, including analgesia, anesthesia and sympathomimetic effect [8]. It produces functional

and electrophysiological dissociation between the cortical and limbic systems of the brain, resulting in a cataleptic state [9]. Owing to its ability to relax bronchial smooth muscle, Ketamine is recommended as an optimizing anesthetic for asthmatic patients and has been clinically used to treat bronchospasm, asthma exacerbation and status asthmaticus [10-12]. In recent years due to its anti-inflammatory properties studies have shown Ketamine plays an important role against lung injury [13].

Various studies in animal tissues have been carried out to determine the mechanism by which Ketamine produces bronchodilation. In a study on canine trachea, significant relaxation of smooth muscle has been seen with an associated decrease intracellular calcium concentration after Ketamine administration [14]. Another study has been performed on tracheal smooth muscle of female guinea pigs which has demonstrated that Ketamine helps in relaxation of smooth muscle fiber inspite of blockade of

Table 5: Various Studies Conducted C Ketamine in Patients of Bronchospasm

Author/Yr	Pt	Age	Study Design	Dose	Duration	Intubation	Measures of Improvement
Fisher 1977 [19]	1	5 yr	Case Report	200 mg iv bolus	bolus	Yes	ABG
Rock et al 1986 [20]	2	4 &10 yr	Case Report	0.5-1 mg/kg (B) 1mg/kg/hr(I)	24 hr	Yes	RR, TV, ABG
Nehama et al 1996 [21]	1	8 months	Case Report	1.4mg/kg(B) 0.2 mg/kg/hr ↓ 0.15 mg/kg/hr	40 hr	Yes	↓ PIP, ↑Pco2, ↑ expansion, ↓ wheeze
Youssef et al 1996 [10]	17	5 mth-17 yr	RCT	2mg/kg (B) 20-60 ì g/kg/m (I)	variable	Yes	Gas xnge Compl.
Petrillo et al 2001 [22]	10	-	POS	1mg/kg (B) 0.75mg/kg(I)	1 hr	No	RR , PEF
Jat KR et al [1]	1	2 months	Case report	1 mg/kg (B) 10-15 ì g/kg/m (I)	48 hrs	No	RR, SPO2, wheezing
Present study	**20**	**2m-24 m**	**POS**	**1mg/kg (B) 10 ì g/kg/m (I)**	**15 hr**	**NO**	**UYAN SCORE, SPO2**

RCT-Randomised Control Study, POS- Prospective Observational Study, ABG-Arterial Blood Gases, RR-Respiratory Rate, TV-Tidal Volume, PIP- Peak Inspiratory Pressure, PEF- Peak Expiratory Flow, SPO2- Oxygen Saturation

nitric oxide synthase by N-omega-nirto-L-arginine methyl ester (L-NAME), a potent NO synthase inhibitor, thus relaxes airway smooth muscle via an epithelial independent mechanism [15]. Other studies on dogs and female guinea pigs showed inhibitory effect of Ketamine on mediator release from mast cells [16] but not to the stimulation of N-Methyl-D-Aspartic acid (NMDA) on tracheal muscles [17]. Thus in spite of all these studies the mechanism by which Ketamine produces airway relaxation is still unclear although it is best attributed to increased catecholamine concentrations, inhibition of catecholamine uptake, voltage-sensitive Ca2+ channel block and inhibition of postsynaptic nicotinic or muscarinic receptors [18].

Several case reports and studies have been conducted on both ventilated and non-ventilated patients who failed to respond to standard therapy. Studies conducted on patients of pediatric age have been shown in Table 5.

Most of these patients have been established cases of bronchial asthma. Expect for a study conducted by Youssef- Ahmed et al (1996) where Ketamine has been used in 17 mechanically ventilated patients with refractory bronchospasm where 4 patients have had respiratory syncytial virus bronchiolitis and 2 patients have had bronchial pneumonia. Improvements in gas exchange, paO_2/FiO_2 ratio and improvements in dynamic compliance have been observed in all the patients [10].

In 2001 Petrillo et al have conducted a prospective observational study in 10 pediatric patients refractory to standard therapy for status asthmaticus and have shown that after Ketamine infusion there has been a significant decrease in clinical asthma score, respiratory rate, oxygen requirement and peak expiratory flow [22]. Howten et al have conducted a double blind placebo controled trial in 53 adult patients and have concluded that intravenous ketamine at low doses demonstrates no increase in bronchodilator effect over standard therapy. This study states that Ketamine is not an adjuvant therapy for patients with acute asthma exacerbation and it does not address the potential efficacy of Ketamine as a medication of last resort [23].

In the present study we have found an improvement in the Uyan score which takes into account five important parameters like respiratory rate, wheezing, retractions, nasal flaring and general status. Thus it implies that the respiratory distress of the patient has relieved and ventilation has improved which is reflected in the improvement of SpO_2.

But some studies have suggested no role of Ketamine in their studies such as; Allen et al (2005) who have conducted a double-blind, randomized, placebo-controlled trial in 68 patients aged 2 to 18 years, with 33 randomized to the Ketamine infusion and 35 randomized to placebo. All patients have received a bolus of 0.2 mg/kg of Ketamine, followed by a 2-hour Ketamine infusion at 0.5 mg/kg per hour or an equal-volume regimen with normal-saline placebo. Authors have concluded that on these doses no incremental benefit has been seen over the standard therapy in this cohort of children with a moderately severe asthma exacerbation [24].

Jat et al (2012) in an intervention review for Ketamine for management of acute exacerbations of asthma in children have found that there is no significant benefit and does not support the case studies and observational reports show-

ing benefits of ketamine in both non-ventilated and ventilated children, and has concluded that "to prove that Ketamine is an effective treatment for acute asthma in children, there is need for sufficiently powered randomised trials of high methodological quality with objective outcome measures of clinical importance" [25]. Ketamine is relatively safe in children and the side effects are generally mild like laryngospasm, emergency reactions, agitation which are self-limiting [26, 27]. The emergence of reactions like confusion, delirium, excitement, hallucinations, irrational behaviour, agitation or pleasant dream-like state may be observed often in older children over 10 years of age and adults, but are very uncommon in younger children [28]. Due to the NMDA receptors antagonistic activity of Ketamine, it may cause apoptosis of newborn brain hence it has been not used in any patient below 2 months of age [29]. The side-effects we have experienced have been increased secretions, tachycardia in all the patients and aspiration in two patients. With the aim of decreasing airway secretions atropine and for prevention of psychologic emergence midazolam can be used, but none of these medications have been used in our study. Limitation of this study has been the inability to test for nasopharyngeal secretions mainly for respiratory syncytial virus due to unavailability of the required test.

Conclusion:

All the studies conducted previously have been mostly in patients of established bronchial asthma with exception of a few. We have conducted the study on patients who presented with wheezing mainly due to bronchiolitis and have been refractory to standard treatment. The use of Ketamine in all patients has been successful and has obviated the need for intubation and mechanical ventilation. The drug has been only used when the other drugs have failed to show a response and the patients have been continuously monitored. Adverse effects of Ketamine may cause harmful effects, hence it is better to use it in a set-up with easy availability of artificial ventilation. And before recommending use of Ketamine routinely a well designed randomized control study needs to be conducted in pediatric age group to ascertain the efficacy and determine the dose in pediatric age group.

References:

1. Jat KR, Azad C, Guglani V. Use of ketamine for refractory wheezing in an infant. *Indian Pediatr* 2012; 49(7):587-588.

2. Reves GJ, Glass Peter SA, Lubarsky DA. Non barbiturate intravenous anesthetics. In: Miller RD, editor. Anesthesia. Philadelphia: Churchill Livingstone, 2000: 240pp.

3. Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. *Anesth Analg* 1966; 45(1): 29-40.

4. Corssen G, Gutierrez J, Reves JG, Huber FC Jr. Ketamine in the anesthetic management of asthmatic patients. *Anesth Analg* 1972; 51(4):588-596.

5. Gateau O, Bourgain JL, Gaudy JH, Benveniste J. Effects of ketamine on isolated human bronchial preparations. *Br J Anaesth* 1989; 63(6): 692-695.

6. Uyan AP, Ozyurek H, Keskin M, Afsar Y, Yilmaz E. Comparison of two different bronchodilators in treatment of acute bronchiolitis. *Internet Journal of Pediatrics and Neonatology* 2003; 3(1).

7. Betts EK, Parkin CE. Use of ketamine in an asthmatic child: A case report. *Anesth Analg* 1971; 50 (3):420-1.

8. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. *Can J Anaesth* 1989; 36(2):186-97.

9. Green SM, Johnson NE. Ketamine sedation for pediatric procedures: part 2, review and implications. *Ann Emerg Med* 1990; 19(9):1033-46.

10. 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 (9):972-976.

11. Sarma VJ. Use of ketamine in acute severe asthma. *Acta Anaesthesiol Scand* 1992; 36 (1):106-107.

12. Heshmati F, Zeinali MB, Noroozinia H, Abbacivash R, Mahoori A. Use of ketamine in severe status asthmaticus in intensive care unit. *Iran J Allergy Asthma Immunol* 2003; 2(4):175-180.

13. Leal Filho MB, Morandin RC, de Almeida AR, Cambiucci EC, Borges G, Gontijo JA, Metze K. Importance of anesthesia for the genesis of neurogenic pulmonary edema in spinal cord injury. *Neurosci Lett* 2005; 373(2):165-170.

14. Pabelick CM, Jones KA, Street K, Lorenz RR, Warner DO. Calcium concentration-dependent mechanisms through which ketamine relax canine airway smooth muscle. *Anesthesiology*; 86(5): 1104-1111.

15. Sato T, Hirota K, Matsuki A, Zsigmond EK, Rabito SF. The relaxant effect of ketamine on guinea pig airway smooth muscle is epithelium-independent. *Anesth Analg* 1997; 84(3):641-647.

16. Hirshman CA, Downes H, *et al*. Ketamine block of bronchospasm in experimental canine asthma. *British Journal of Anaesthesia*. 1979; 51: 713.

17. 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(6):1383-8.

18. Hirota K, Lambert DG. Ketamine: its mechanism(s) of action & unusual clinical uses. *Br J Anaesth* 1996; 77(4): 441–444.

19. Fisher MM. Ketamine hydrochloride in severe bronchospasm. *Anesthesia* 1977; 32(8): 771.

20. 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(5):514-516.

21. 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(4):294-297.

22. Petrillo TM, Fortenberry JD, Linzer JF, Simon HK. Emergency department use of ketamine in pediatric status asthmaticus. *J Asthma* 2001; 38(8):657-664.

23. 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(2):170-175.

24. Allen JY, Macias CG. The efficacy of ketamine in pediatric emergency department patients who present with acute severe asthma. *Ann Emerg Med* 2005; 46(1):43-50.

25. Jat KR, Chawla D. Ketamine for management of acute exacerbations of asthma in children. *Cochrane Database Syst Rev* 2012; 11:CD009293.

26. Parker RI, Mahan RA, Giugliano D, Parker MM. Efficacy and safety of intravenous midazolam and ketamine as sedation for therapeutic and diagnostic procedures in children. *Pediatrics* 1997; 99(3):427–431.

27. Roback MG, Wathen JE, Bajaj L, Bothner JP. Adverse events associated with procedural sedation and analgesia in a pediatric emergency department: a comparison of common parenteral drugs. *Acad Emerg Med* 2005; 12(6):508-513.

28. Sherwin TS, Green SM, Khan A, Chapman DS, Dannenberg B. Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. *Ann Emerg Med* 2000; 35(3):229-238.

29. Mellon RD, Simone AF, Rappaport BA. Use of anesthetic agent in neonates and young children. *Anesth Analg* 2007; 104(3): 509-520.

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