Original Article

Ketamine versus aminophylline for acute asthma in children: A randomized, controlled trial

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Abstract:

BACKGROUND: There is a lack of consensus regarding second-line therapy in children with acute asthma who fail to the standard therapy. Ketamine had bronchodilator property and may be useful in the treatment of acute asthma.

OBJECTIVE: The objective of this study was to evaluate the efficacy and safety of ketamine as compared to aminophylline in children with acute asthma who respond poorly to the standard therapy.

METHODS: This randomized controlled trial included patients with acute asthma having Pediatric Respiratory Assessment Measure (PRAM) score ≥5 at 2 h of standard therapy. The enrolled patients received either intravenous (IV) ketamine or IV aminophylline. Primary outcome measure was change in PRAM score at the end of intervention. Secondary outcome measures included adverse effects, change in PO_2 and PCO_2, need for mechanical ventilation, and duration of hospital stay.

RESULTS: The trial included 24 patients each in ketamine and aminophylline groups. The baseline parameters were similar between the groups. The primary outcome was similar in both the groups with a change in PRAM score of 4.00 ± 1.25 and 4.17 ± 1.68 (P = 0.699) in ketamine and aminophylline groups, respectively. The secondary outcomes were not different between the groups.

CONCLUSION: Ketamine and aminophylline were equally effective for children with acute asthma who responded poorly to the standard therapy.

Key words:

Acute asthma, aminophylline, children, ketamine

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The trial is registered at the Clinical Trials Registry - India with number as CTRI/2013/09/004000. Available at: http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=4308&EncHid=& userName=CTRI/2013/09/004000.

Acute exacerbation of asthma is responsible for frequent emergency department visits in children. The initial standard therapy for acute asthma includes oxygen supplementation, nebulized beta-2 agonist with or without ipratropium bromide, and corticosteroids (oral or parenteral).[1-3] A subset of children with acute exacerbation has a poor response to initial treatment and requires second-line therapy. The second-line adjuvant therapy may include magnesium sulfate, aminophylline, intravenous (IV) beta-2 agonist, or helium-oxygen, but there is no consensus among asthma care providers regarding the superiority of one treatment modality over the other. A small proportion of hospitalized children with acute asthma even fails to respond to this second-line adjuvant therapy and may need mechanical ventilation.

Ketamine, a phencyclidine-derived drug, is used frequently in children for procedural sedation and analgesia.[4] Adverse effects of ketamine in children are minor, infrequent, and mostly, self-limiting.[5-7] Ketamine had sympathomimetic activity and may relieve bronchospasm.[8] Many case reports, case series, and observational studies had shown the efficacy of ketamine in acute exacerbation of asthma in children who failed to initial therapy.[6,7,9,10] Aminophylline is a competitive nonselective phosphodiesterase inhibitor that increases intracellular cyclic adenosine monophosphate, inhibits tumor necrosis factor-alpha and leukotriene synthesis, and causes bronchodilatation.[11] Aminophylline, when added to the standard therapy for acute

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exacerbation of asthma in children, improved lung function within 6 h of treatment; however, there was no apparent reduction in symptoms and duration of hospital stay. There is insufficient evidence for aminophylline for the impact on oxygenation, pediatric Intensive Care Unit (PICU) admission, and mechanical ventilation. Aminophylline use was associated with a significant increased risk of vomiting.[12] The standard therapy includes the use of oxygen supplementation, inhaled short-acting beta-2 agonist, ipratropium bromide, systemic steroids (if exacerbation is moderate to severe), and magnesium sulfate (if poor response even after adding systemic steroids).

Ketamine may be a potential therapy for acute asthma in children, but there is a lack of randomized controlled trials (RCTs). The objective of this study was to evaluate the efficacy and safety of ketamine as compared to aminophylline for improvement in Pediatric Respiratory Assessment Measure (PRAM) score[13] in children with moderate-to-severe acute exacerbation who responded poorly to the standard initial therapy.

Methods

Trial design

It is a randomized, open-label, controlled trial conducted at a tertiary care center in North India for 1 year. Consent was taken from parents before enrollment in the study. The institute's Ethics Committee approved the study.

Participants

The consecutive patients presenting to pediatric emergency room with acute exacerbation of asthma were assessed for eligibility. Children of 1–12 years of age with acute moderate-to-severe exacerbation of asthma having PRAM score ≥5 at 2 h of the standard therapy were eligible for inclusion in the study. Treating physician diagnosed asthma in pediatric emergency room. The study person was informed by mobile phone once the diagnosis of acute asthma was made, and he/she was available within minutes to enroll the patient. Patients with a history of prematurity, bronchopulmonary dysplasia, co-existing primary parenchymal pulmonary disease other than pneumonia due to asthma itself (e.g., cystic fibrosis), or co-existing congenital/acquired heart diseases were excluded from the study. Similarly, patients with known hypertension, known allergy to ketamine or aminophylline, and patients with raised intracranial pressure were excluded from the study.

Interventions

All children with acute exacerbation of asthma received initial standard therapy: Oxygen supplementation; salbutamol nebulization, 0.15 mg/kg (minimum 2.5 mg) for every 20 min for 1st h and then 0.5 mg/kg (maximum 10 mg) for every 1 h; ipratropium nebulization 0.5 mg/dose, for every 20 min for 1st h, and then 0.5 mg/dose 6 hourly if needed; and systemic steroids, 10 mg/kg of hydrocortisone loading followed by 2.5 mg/kg 6 hourly, if needed. The PRAM score was monitored for every 30 min. The PRAM score[13] included five parameters, namely, suprasternal retractions, scalene muscle contraction, air entry, wheezing, and O_2 saturation, with a score of 0–2 or 3 for each item. The total score ranged from 0 to 12 with a score of <5 indicating mild exacerbation, score of 5–8 indicating moderate exacerbation, and score of ≥9 indicating severe exacerbation of asthma. If PRAM score remained ≥5 at 1 h of therapy, IV magnesium sulfate 25 mg/kg over 30 min was given. The patients were eligible for enrollment in the study, if PRAM score remained ≥5 by the 2 h of standard therapy. The enrolled patients were randomized to one of the two following groups: (1) IV ketamine at a dose of 0.5 mg/kg bolus over 20 min, followed by continuous infusion of 0.6 mg/kg/h for 3 h; (2) IV aminophylline 5 mg/kg bolus over 20 min followed by the continuous infusion of 0.9 mg/kg/h for 3 h. The 3 h were chosen based on the previous studies where ketamine was used for 3 h. Standard therapy was continued during the study period. Treating physician decided further management after the study ended at 3 h of intervention.

Outcomes

Primary outcome measure was change in PRAM score from enrollment to the end of the intervention. Secondary outcome measures included adverse effects (vomiting, arrhythmias, hypotension, hypertension, dysphoric reactions, and oral secretions), change in PO_2 and PCO_2, change in peak expiratory flow (PEF), need for mechanical ventilation, and duration of hospital stay.

Data collection

Enrolled patients were monitored throughout the study period by one of the investigators. Demographic data were collected from all the patients. PRAM score as well as vital parameters were recorded at 30, 60, 120, and 180 min and then at 6, 12, and 24 h. Arterial blood gas was performed at enrollment and at 180 min. PEF was performed at enrollment and at 180 min in patients above 5 years of age who were able to perform the procedure, and the best of three attempts was considered for analysis. Patients were monitored for any side effect, especially vomiting, arrhythmias, hypotension, hypertension, dysphoric reactions, and oral secretions.

Sample size

The sample size was calculated as 24 patients in each group to detect a difference of 2 points in PRAM score at a significance level of 0.05 and a power of 80% ($\beta = 0.20$). The standard deviation (SD) for PRAM score was considered 2.46 based on the previous published literature.[13]

Randomization: Sequence generation

Block randomization was administered where random numbers were generated using a web-based random number generator. A person not involved in the enrollment of patients generated the random numbers.

Allocation concealment mechanism

The random number sequences were placed in serially numbered, opaque, sealed envelopes. Envelopes were opened after taking consent from eligible patients.

Blinding

The patients and treating team were not blinded to the intervention, though the person who assessed the outcome was blinded to the intervention.

Statistical methods

The continuous variables were presented as mean ± SD and dichotomous data as percentage. The continuous data were compared between the groups using Student's *t*-test for normally distributed data and Mann–Whitney U-test test for skewed data. The dichotomous data were compared using Chi-square test. The analysis was done as intention-to-treat. Continuous variables that had multiple measures obtained over time were analyzed by repeated measure analysis of variance (ANOVA) for between-group and within-group differences. Statistical analysis was done using SPSS Inc., released 2007; SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 210 patients were presented to pediatric emergency department with acute exacerbation of asthma during the study period. All patients were assessed for eligibility and 162 were excluded because the PRAM score was <5 at 2 h of standard therapy. Forty-eight patients were included in the study. Out of these, 24 received ketamine and 24 received aminophylline. All patients completed the intervention and were included in the analysis [Figure 1].

The median (interquartile) age of total (48) patients was 48.0 (24.2, 72.0) months (range: 16–144 months). There were 20 (41.7%) male and 28 (58.3%) female patients. Baseline demographic data and PRAM score were similar between both the groups [Table 1].

Primary outcome: Pediatric Respiratory Assessment Measure score

The change in PRAM score from enrollment to 3 h of intervention was similar in ketamine and aminophylline groups [Table 2]. Overall, PRAM score decreased significantly from enrollment to 3 h of intervention (7.88 ± 1.61 vs. 3.83 ± 1.86; mean difference 4.04; 95% confidence interval [CI] 3.61,4.47; P = 0.000). The

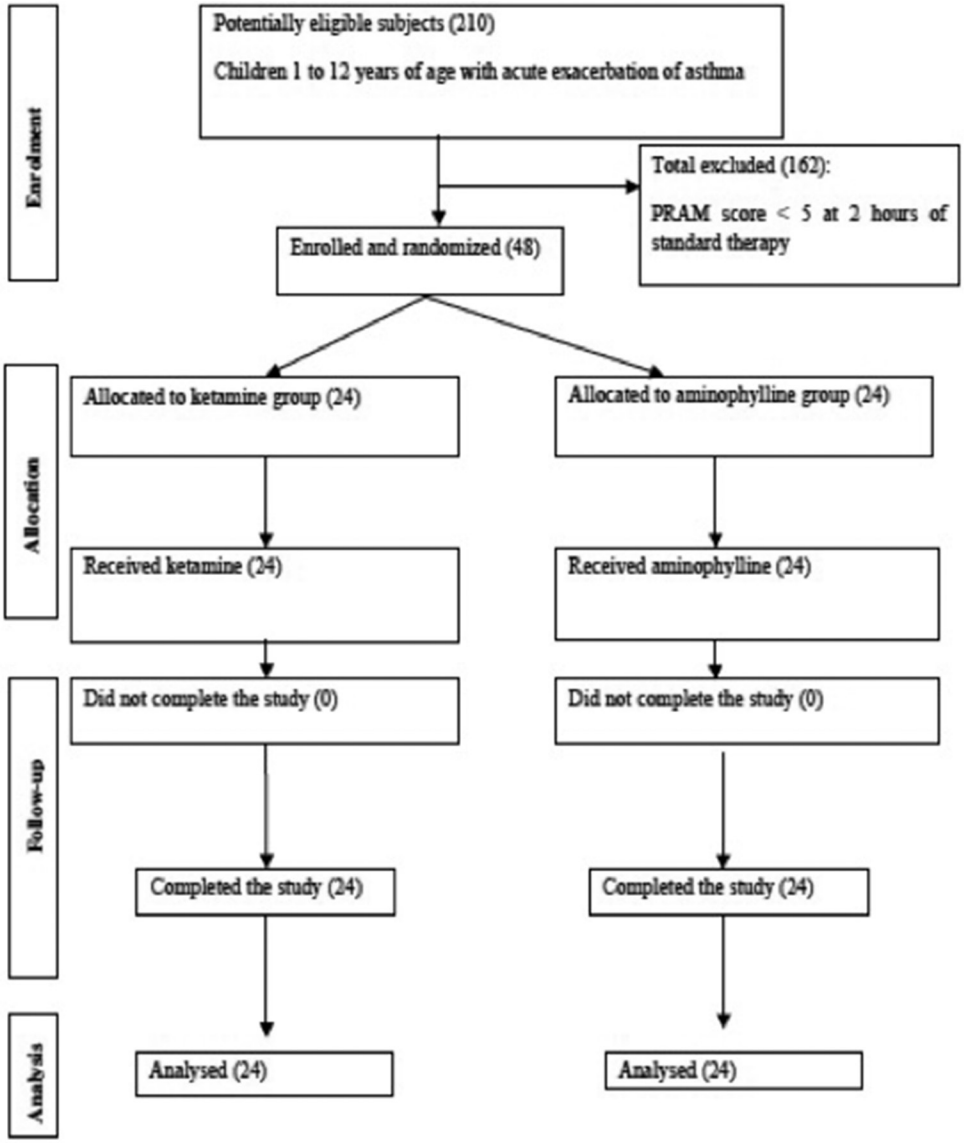

Figure 1: Patient flow diagram

Table 1: Baseline parameters between ketamine and aminophylline groups

Parameter	Ketamine group (*n*=24)*	Aminophylline group (*n*=24)*	*P*
Male:female (*n*)	12:12	8:16	0.380
Urban:rural (*n*)	18:6	14:10	0.359
Number of patients on regular ICS	9/24	8/24	1.000
Number of patients with *Z*-score for weight/age below 2	1/24	0/24	0.478
Number of patients with *Z*-score for height/age below 2	1/24	1/24	1.000
Tachycardia at enrollment	23/24	21/24	0.489
Body mass index	14.98±1.51	14.27±1.48	0.111
Age (months; median [IQR])	42.0 (22.0-72.0)	60.0 (24.2-72.0)	0.468
Duration of cough before presentation (days)	2.78±2.19	2.29±1.36	0.360
Duration of breathlessness before presentation (days)	1.29±0.75	1.17±0.56	0.518
Age of onset of symptoms (months)	27.38±28.80	21.46±18.74	0.403
Number of emergency visit in last 1 year	5.88±2.67	5.96±3.81	0.828
PRAM score at presentation	9.36±1.59	9.60±1.31	0.604
PRAM score at enrollment	7.71±1.68	8.04±1.55	0.478
SpO_2 at room air (%) at enrollment	89.33±5.31	89.42±3.55	0.949

*Mean±SD, unless specified, IQR. IQR = Interquartile range, SD = Standard deviation, PRAM = Pediatric Respiratory Assessment Measure, ICS = Inhaled corticosteroids

Table 2: Outcome measures between ketamine and aminophylline groups

Parameter	Ketamine group*	Aminophylline group*	Mean difference	95% CI	*P*
Primary					
Change in PRAM score (0-3 h)	4.00±1.25	4.17±1.68	−0.17	−1.02,0.69	0.699
Secondary					
Change in PO_2 (0-3 h, mmHg)	24.15±24.07	23.83±31.59	0.32	−16.62, 17.26	0.970
Change in saturation (SpO_2) (0-3 h)	5.42±3.36	4.71±2.35	−0.71	−0.98,2.39	0.402
Change in PCO_2 (0-3 h, mmHg)	−1.29±6.49	−2.27±6.52	0.99	−2.92,4.90	0.614
Duration of hospital stay (days)	3.50±1.28	3.25±1.07	0.25	−0.44,0.94	0.468
Hypertension at any time (*n*)	2/24	0/24			0.489

*Mean±SD, otherwise specified, CI. CI = Confidence interval, SD = Standard deviation, PRAM = Pediatric Respiratory Assessment Measure

PRAM score decreased significantly in both the ketamine (from 7.71 ± 1.68 to 3.79 ± 1.84; mean difference 3.92; 95% CI 3.39,4.44; $P = 0.000$) and aminophylline (from 8.04 ± 1.55 to 3.88 ± 1.92; mean difference 4.12; 95% CI 3.46,4.87; $P = 0.000$) groups. At 3 h of intervention, the PRAM score was similar between the groups (3.79 ± 1.84 vs. 3.88 ± 1.92; mean difference 0.08; 95% CI −1.18,1.01; $P = 0.879$).

Repeated measures analysis of variance

The PRAM score was measured at enrollment, then at 30 min, 60 min, 120 min, 180 min, and finally, at 24 h after intervention. When using an ANOVA with repeated measures with a Greenhouse-Geisser correction, the mean PRAM scores at different time periods were significantly different (F [2.580, 118.658] = 201.092, $P < 0.0005$). Bonferroni *post hoc* test suggested that the differences in PRAM score were significant between each time period it was measured [Table 3 and Figure 2]. At each time period, the PRAM score was not statistically different between the ketamine and aminophylline groups [Table 3].

Table 3: Pediatric Respiratory Assessment Measure score at enrollment, during intervention, and later on

Time	Total participants* (*n*=48)	Ketamine group* (*n*=24)	Aminophylline group* (*n*=24)	*P*
At enrollment (0 min)	7.88±1.61	7.71±1.68	8.04±1.55	0.478
30 min	7.58±1.64	7.46±1.62	7.71±1.68	0.602
60 min	6.44±1.64	6.42±1.69	6.46±1.62	0.931
120 min	5.27±1.67	5.08±1.67	5.46±1.69	0.443
180 min	3.83±1.86	3.79±1.84	3.88±1.92	0.879
24 h	0.26±0.65	0.25±0.75	0.27±0.55	0.907

*Mean±SD

Secondary outcomes

Side effects

Hypertension (at any time) was observed in two patients in ketamine group whereas no hypertension event was observed in aminophylline group ($P = 0.489$) during the intervention period. At the enrollment and after 3 h of intervention, all the patients were normotensive in both groups. At the enrollment, tachycardia was noticed in 23 and 21 patients in ketamine and aminophylline groups, respectively ($P = 0.489$). Tachycardia was still present in 22 and 19 patients in ketamine and aminophylline groups, respectively ($P = 0.346$), at the 3 h of intervention. There were no other adverse effects in both the groups except for one episode of vomiting in one patient from ketamine group.

The change in PO_2, PCO_2, and oxygen saturation from enrollment to the end of intervention was similar between

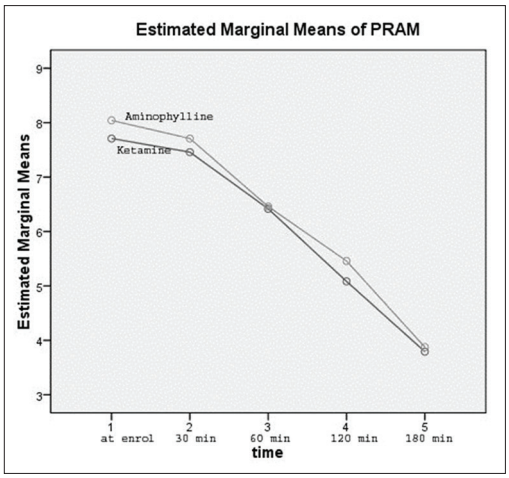

Figure 2: Mean Pediatric Respiratory Assessment Measure score from enrollment to 3 h of intervention

ketamine and aminophylline groups [Table 2]. The data for PEF were not analyzed, as only 11 patients were able to perform the procedure at the enrollment due to the severity of exacerbation. No child required intubation and mechanical ventilation in the study. All the enrolled patients were discharged from the hospital after recovering from exacerbation except one patient who left the hospital against medical advice because of personal reasons. The duration of hospital stay was similar between the groups [Table 2].

Discussion

The present RCT demonstrated an equal efficacy of ketamine and aminophylline for acute asthma in children who failed standard therapy. Betts and Parkin first used ketamine successfully in an asthmatic child in 1971.[14] Since then, there had been several case reports and small case series of successful use of ketamine for relieving bronchospasm in children with acute asthma exacerbation.[6,9,10,15,16]

Petrillo *et al*.[7] used ketamine (IV loading dose of 1 mg/kg/h, followed by a continuous infusion of 0.75 mg/kg/h for 1 h) in a prospective observational study for ten children with status asthmaticus who were unresponsive to standard treatment. They found that clinical asthma score improved significantly after starting ketamine. However, they observed side effects of ketamine in four out of ten patients.[7] The adverse effects may be due to higher dose of ketamine than our study. A previously published RCT by Allen and Macias[17] randomized 68 children with acute asthma to receive either ketamine (n = 33) as IV bolus of 0.2 mg/kg, followed by a 2 h infusion at 0.5 mg/kg/h or an equal volume of normal saline placebo (n = 35). The efficacy was assessed by Pulmonary Index Score (PIS) and found that ketamine was not beneficial over standard therapy. They did not observe any side effect of ketamine.[17] The lack of benefit of ketamine in the study may be because of lower dose of ketamine as compared to our study and other studies. The acute asthma severity score used was different (PIS vs. PRAM) in this study and our study. A placebo-controlled RCT in adults used ketamine at a dose of 0.1 mg/kg bolus, followed by 0.5 mg/kg/h infusion for 3 h, found that the studied outcomes were similar between the ketamine and the placebo groups.[18] In the same study, the initial bolus dose was 0.2 mg/kg, but it was later decreased to 0.1 mg/kg due to dysphoric reactions. In another RCT in adults, a 1 mg/kg ketamine dose was used on mechanically ventilated patients; the ketamine group had improved wheezing, PO_2, and PCO_2 as compared to placebo.[19] A recent Cochrane review found only one RCT of ketamine in the treatment of acute asthma in children and concluded that there is a need for more RCTs on ketamine.[20]

Ketamine had been used in a bolus dose ranging from 0.1 mg/kg to 2 mg/kg and in infusion dose ranging from 0.15 mg/kg/h to 2.5 mg/kg/h in different observational and clinical trial studies.[21] Similarly, duration of infusion also varied from 1 h to 5 days.[21] Further trials on ketamine in acute asthma exacerbation should explore an appropriate dose of ketamine that is sufficient to cause bronchodilatation, but without significant side effects. There is no study in the past which compared ketamine and aminophylline. In a Cochrane review regarding aminophylline for acute asthma exacerbation in children, where eight trials were included, it was found that aminophylline when added to standard therapy for acute exacerbation of asthma in children improved lung function within 6 h of treatment; however, there was no apparent reduction in the symptoms and duration of hospital stay. There was insufficient evidence for aminophylline for the impact on oxygenation, PICU admission, and mechanical ventilation. Aminophylline use was associated with a significant increased risk of vomiting, but no difference in hypokalemia, headaches, tremor, seizures, arrhythmias, and deaths.[12]

There are limitations too in the present study. Ideally, ketamine should have been compared with placebo to observe the effect. We did not use placebo in the controlled arm because our Ethics Committee did not allow placebo arm as we enrolled the patients with moderate–to-severe exacerbation of asthma who failed to respond to standard therapy including magnesium sulfate, and use of placebo in such situation might not be justifiable. Further, the treating team and patients were not blinded to the intervention, though outcome assessor was blinded to the intervention. Another limitation is this is a single-center study. There were six patients below 2 years of age, and we did not perform any viral study on them.

Conclusion

Ketamine is equally efficacious as compared to aminophylline for acute asthma in children who respond poorly to standard therapy.

The trial is registered at the Clinical Trials Registry-India with number as CTRI/2013/09/004000. Available at: http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=4308&EncHid=&userName=CTRI/2013/09/004000.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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