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Research Article

A Prospective, Randomized Controlled Trial of Noninvasive Ventilation in Acute Exacerbation of Asthma in Children

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Abstract
Objective: *To compare the benefits of noninvasive ventilation (NIV) plus standard therapy vs standard therapy alone in children with acute exacerbation of asthma.*
Design: *Randomized control trial.*
Setting: *Tertiary care Pediatric Intensive Care Unit (PICU), duration of study from October 2014 to September 2016.*
Participants: *Three month to twelve years with acute severe asthma (<24 hours) with initial Becker Score >7 were eligible for this study.*
Interventions: *The study group received NIV under inspiratory positive airway pressure ranging between 10 cm - 18 cm H2O, expiratory positive airway pressure between 4 cm - 12 cm H2O. Vital signs, PO2, PCO2, pH, SPO2 , becker score were recorded at the start, 1, 2, 4, 12, 24, and 48 hrs into the study.*
Result: *Heart rate after four hour and twelve hour and respiratory rate after two hour of treatment were significantly lower compared with admission (p = 0.0001 and p = 0.0294, respectively). With NIV, PO2 at four hour, SPO2 at two hour improved significantly. The endotracheal intubation was significantly lower (22%) in the NIV group than in the control group (45%; p = 0.01698).There was significant difference in length of stay in PICU (p= 0.0109) and hospital (p = 0.0115).*
Conclusion: *NIV seems to afford these children protection from endotracheal intubation and reduced in length of stay in PICU and hospital.*
Keywords: *Non Invasive Mechanical Ventilation, Asthma.*

Introduction

NIV refers to a technique of respiratory support that is provided without an artificial airway in the trachea[(1)]. Indications of use of NIV are obstructive lower airway disease like Bronchiolitis or Bronchial asthma, acute hypoxemic respiratory

failure and cardiogenic pulmonary edema[2]. If untreated they culminate into hypoxemic respiratory failure. It has been shown in previous studies that Continuous Positive Airway Pressure (CPAP) is of benefit in asthmatic attacks induced by histamine and methacholine [3,4] and reduce respiratory distress in acute asthma [5]. Now there is increasing evidence that Bilevel Positive Airway Pressure or CPAP can be very beneficial in acute lower respiratory obstructive conditions [6-13].

Methods

All children aged between twelvemonth to twelve year were admitted in PICU with acute severe asthma (<24 hours) [acute exacerbation of asthma not controlled with inhaled beta 2 agonists, moist oxygen inhalation and steroids (45)] with initial Becker Score>7. Newly admitted patients with history of cough and respiratory distress or known case of asthma, who were potentially dyspneic were identified from daily OPD, Emergency, ward and PICU. A two stage consent process was utilized by first asking patients if aged 7 years or more and their parents or caregiver, for their permission to screen them for study eligibility. Eligible 80 children were recruited; 40 children were randomly allocated to noninvasive inspiratory positive airway pressure and expiratory positive airway pressure plus standard therapy (study group); the remaining 40 were given standard therapy (Control group). Both groups were comparable in demographic.

Children who were not able to maintain their airway protective reflexes, those having thick trachea-bronchial secretion, any mid-face abnormality (i.e. maxillary hypoplasia, small chin), Vasoactive Inotrope score >10 (i.e. Injection Dopamine >10mcg/kg/min) at the time of PICU admission were excluded from the Study. Gaies et al [14] published the Vasoactive Inotrope Score in 2010, because the previous Inotrope Score went out of favor with the increasing use of newer vasoactive-inotrope agents in PICU.

Study was conducted in PICU from October 2014 to September 2016. All children who met the above criteria were assessed for the cause of wheeze. Children with acute severe asthma or the episode of acute onset wheeze thorough elicitation of history from parents, clinical presentation and examination, made the diagnosis of bronchial asthma very likely according to the criteria laid down by British Thoracic Society were treated with nebulized Salbutamol at twenty minutes interval for at least four times. Baseline arterial blood gas values were derived in all children during the ongoing first nebulization. All patients received oxygen @ 2-4 litre/minute with face mask to keep saturation ≥ 94%. Salbutamol infusion (0.6mcg-1mcg/kg/min) were started. Nebulization with Ipratropium bromide and Intravenous hydrocortisone (10mg/kg first dose followed by 5 mg/kg every 6 hrs) were added as adjunct if felt necessary. Children, who did not respond with back to back nebulization received Injection Magnesium Sulphate (40-60mg/kg). All patients were fed through nasogastric tube and received physical therapy four times a day, as required. Patients in the control group received neither NIV nor sedation. Study group received standard treatment plus NIV. All children were put on NIV with an appropriate size nasal mask/facemask and held in place with head straps. A patch was placed on the skin of the nasal bridge to prevent facial sores. Bed heads were kept raised by 45` to prevent aspiration. Ketamine as intravenous bolus dose (1 mg/kg) or intravenous infusion (0.5-2mg/kg/hr)/ Triclofos sodium with dose 20mg/kg every 6 – 8 hourly by mouth, were administered in case of poor tolerance to NIV.

Maquet servo- I ventilators with facilities of NIV, inline nebulization and close loop suction were used Pressure of four cm of H_2O, Peak Inspiratory Pressure of ten cm of H_2O, respiratory rate according to the age of the child, Fio2 of 0.5. Ventilation parameters were gradually titrated depending upon the Spo2 and Po2 value.

The children were continuously monitored by one dedicated investigator for respiratory rate bilateral

air entry and wheeze, work of accessory muscles, sensorium, Becker Score. If there was no improvement or worsening of the above parameters at the end or during the ongoing treatment, children were put on NIV. Therapeutic goals were set as1) Decreased respiratory rate according to age, 2) Decreased work of accessory muscles of respiration, 3) Improvement in bilateral air entry and decreased wheeze. 4) Improvement of sensorium, 5)Improvement of Becker, 6)$SPO_2 \geq 95\%$ as measured by Pulse-oximetry, 7) $PO_2 \geq 70$ mm of Hg, PCO_2 of ≤ 70 mm of Hg was considered acceptable if pH was > 7.2. Data collection after starting of NIV (zero hours) was assessed every hour and following parameters were collected- Becker score, respiratory rate, heart rate, SPO_2, PO2, PCO2, Ph, work of breathing, air-entry in chest and wheeze, and level of consciousness. Arterial blood gas values were obtained after two hour, four hour of initiating NIV, and then every eight hourly. Blood gas values were also done thirty minutes after doing any necessary change in ventilator settings.

As few parameters of Becker score and assessment of bilateral air entry and wheeze were subjective parameters, they were recorded by the dedicated investigator and cross checked thereafter by another person. SPO_2 was measured by pulse oximetry, partial pressure of Oxygen (PO_2) and carbon-dioxide (PCO_2) was measured by arterial blood gas (ABG) by OPTI-CCA Blood gas analyzer. For assessment of level of consciousness we used Modified Glasgow Coma Scale (GCS) for infants and children.

This clinical trial was acknowledged at Clinical Trials Registry – India (www.ctri.nic.in), acknowledged no. REF/2015/06/009136 and Registry No. CTRI/ 2017/02/007854

Results

For statistical analysis data were analyzed by SPSS 20.0.1 and Graph Pad Prism version 5. The Student's independent sample's t-test was applied to compare normally distributed numerical variables between groups; unpaired proportions were compared by Chi-square test or Fischer's exact test. Eighty patients were enrolled with forty in study group and forty in control groups respectively. Demographic and initial physiologic parameters were similar in both groups (Table 1).Patients were 12–94 months old, with a median of eighteen months in the control group and sixteen months in the study group.

The mean age of patients was 35.9250 ±22.7285 monthsin study group vs37.1500 ±21.5056 months in control group which was not statistically significant (p=0.8051). Heart rate at four hours of patients was 137.5750 ±14.7264 beats per minute (bpm) in study group hvs 151.5750±13.7111 bpmin control group (Table 1) which was statistically significant (p=0.0001). Respiratory Rateat two hours of patients was 50.7750 ±9.6277 per minute (pm) in study group and 55.7250±10.3080 pm in control group which was statistically significant (p=0.0294). SPO2 at four hours was 93.500 ±7.3238in study group and 876500±5.3711% in control group (Table 2) which was statistically significant (p=0.0001,). PO2 at four hours was 92.0000±25.7493% and 78.2000±24.2679% in study and control group respectively which was statistically significant (p=0.0158).In study group thirty (80%) patients did not require intubation and eight 20%) patients needed intubation. In Control group twenty two (55%) patients required no intubation and eighteen (45%) patients needed intubation (Fig. 1). Association between intubation rate in two group was statistically significant (p=0.01698). The hospital stay was 7.5000±2.9526 days in control group vs 6.0750 ±1.8451 days in study group which was statistically significant (p=0.0115). The mean PICU stay was 2.9250 ±1.4031 days in study group vs 3.9250±1.9792 daysin control group. Difference of mean PICU stay in two groups was statistically significant (p=0.0109).

Table 1: Baseline demographic and physiological parameters (median)

	Control Group (n = 40)	Study Group (n = 40)	P value
Male:female	22:18	27:13	0.2511
Age (months)	28 (14 – 96)	24.5 (12 – 94)	0.8051
Heart rate (beats/min)	160 (140 – 180)	171.5 (147 – 194)	0.1685
Respiratory rate (breaths/min)	60 (39 – 72)	58 (36 – 78)	0.5066
Becker score	11 (9 – 11)	11 (9- 11)	0.2077
pH	7.25 (7.21 – 7.37)	7.31 (7.2 – 7.41)	0.0635
PO2 (mm Hg)	55.5 (45 – 175)	58 (45 – 218)	0.2008
PCO2 (mm Hg)	36 (4 – 64)	35 (21 – 60)	0.1218
SPO2 (%)	86.5 (77 – 94)	87.5 (73 – 96)	0.8580

Table 2: Distribution of MEAN PICU Stay days in two groups

Group	Number	Mean	StdDev	Minimum	Maximum	Median	p-value
Control Group	40	3.9250	1.9792	2.0000	8.0000	3.0000	0.0109
NIV Group	40	2.9250	1.4031	2.0000	7.0000	2.0000	

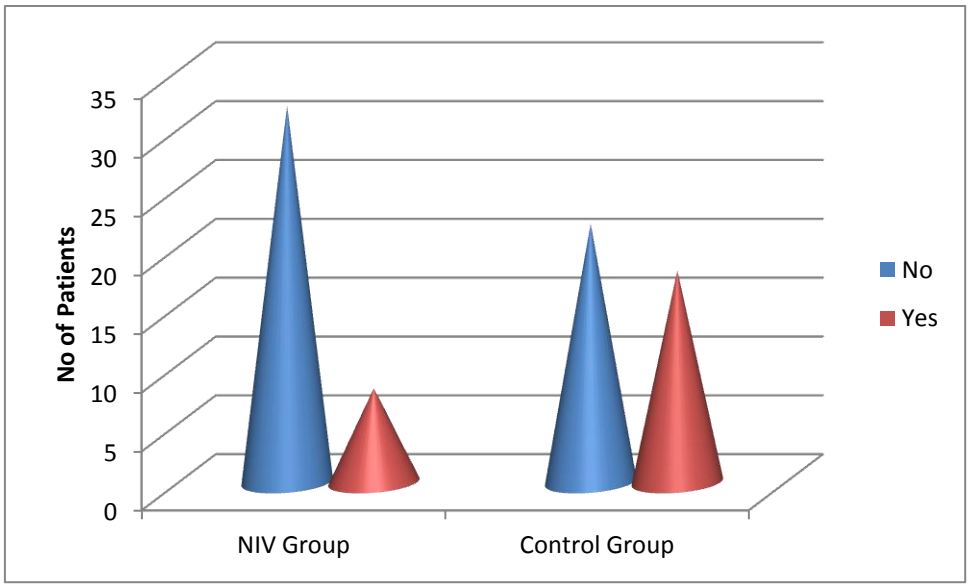

Fig. 1: Showing Intubation rate in 4hrs in two groups.

Difference of mean hospital stay in two groups was statistically significant (p=0.0115).

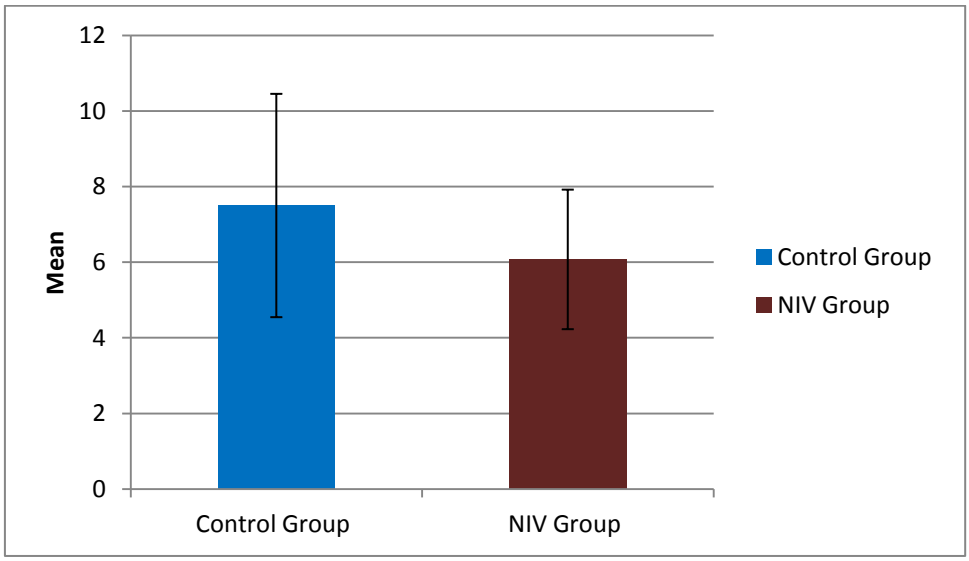

Fig.2: Showing the mean hospital stay in both group

Discussion

The prevalence and severity of asthma and other diseases characterized by acute lower airway obstruction has increased in recent years, despite increased understanding of the pathophysiology of these diseases and development of new therapies[14]. Conventional therapy for acute exacerbations of asthma and other diseases characterized by lower airway obstruction is directed at relieving bronchoconstriction, decreasing airway inflammation, and clearing airway mucus. However, in some patients, maximal medical therapy is inadequate. Persistent airway obstruction reduces respiratory muscle mechanical efficiency and endurance, and the likelihood of fatigue and respiratory failure is increased [15]. Historically, it has been shown that use of positive airway pressure in adult population is beneficial in both acute and chronic respiratory insufficiency. Inspiratory Positive Airway Pressure and Expiratory Positive Airway Pressure improve hypercapnia and hypoxemia. Hypoxemia is the result of alveolar hypoventilation (with increased CO2) and altered ventilation/perfusion ratio. It is treated by increasing oxygen concentration and recruiting airspaces[16]. Positive pressure improves tidal volume, gas exchange, respiratory frequency, and diaphragm activity in both chronic respiratory failure [17-19] and Acute Lung injury[20], proportionate to the level of applied pressure.

The use of positive airway pressure in patients with airway obstruction has been discouraged because of concerns of worsening lung hyperexpansion. The use of positive end-expiratory pressure in intubated adult patients with asthma was associated with increases in static lung volumes[21]. Despite of above facts Inspiratory and Expiratory Positive Airway Pressure has been proved to be extremely effective in hypoxemic respiratory failure secondary to multiple causes like pneumonia, cardiogenic pulmonary edema, postsurgical respiratoty failure. Positive airway pressure decreases work of breathing, improves diaphragmatic contractility, reduced respiratory rate, heart rate and there was significant improvement in gas exchange. In maximum studies investigators were able to avoid endo-tracheal intubation and invasive ventilation [22-24]. In spite of adequate data is available regarding use of NIV in adult population Pediatric data is still lacking. There are descriptive studies regarding use of NIV in children with acute lower airway obstruction. In maximum cases positive airway pressure was provided either by CPAP or by BiPAP [25]. In a systematic review concluded that NIV plus standard treatment in Acute Hypoxemic Respiratory Failure reduced the need for intubation by 23%. In this series, the youngest children had more intubation in both groups. This result might be explained by the fact that infants may respond less to NIV because of weaker muscles, narrower airway, and greater difficulty in handling secretions despite adequate respiratory physiotherapy. In a previous study of NIV in children with hypoxemic respiratory failure, Padman et al. excluded children of less than six months of age from their study.

However in our study we used NIV in children 12 months to 94 month of age. In our study the mean age of patients was statistically significant (p=0.8051).Unlike maximum previous studies in children we used pressure control mode to provide positive inspiratory and expiratory pressure. Tolerance of NIV mask was not a problem in our study as we used Ketamine infusion (0.5-2mg/kg/hr) for sedation and analgesia based upon the different clinical situation. Although use of ketamine showed some beneficial effect in our study it should be used in great caution particularly in infancy. Abdominal distension was also not a problem as we routinely used oro-gastric tube during NIV administration. Hemo-dynamic compromise (i.e hypotension, prolong CRT, or shock) or pulmonary air leak (i.e. Pneumothorax, pneumo-mediastinum) were also not seen in any of the children recruited for this study.

NIV in our study showed excellent results in children with acute exacerbation of asthma. There was improvement of heart rate at four hours (137.5750 ±14.726 bpm vs 151.5750± 13.7111bpm) in study group vs control group respectively. Respiratory rate at two hours (50.7750 ±9.6277 pm vs 55.7250±10.3080pm) in study vs control groups. Work of breathing along with SPO2 and PO2 was 93.500 ±7.3238vs 876500±5.3711% (p=0.0001) and 92.0000±25.7493% vs78.2000 ±24.2679% (p=0.0158) in study vs control groups. In study group eight (20%) patients were intubated aginst eighteen (45%) in control group. Association between intubation rate in two group was statistically significant (p=0.01698). In Control Group, the mean hospital stay was 7.5000±2.9526 days vs6.0750 ±1.8451days in study group. Difference of mean hospital stay was statistically significant (p=0.0115). In study Group, the mean PICU stay was 2.9250 ±1.4031 days. In Control Group, the mean PICU stay was 3.9250 ±1.9792 days which is statistically significant (p=0.0109).

NIV applied to children suffering from acute exacerbation of asthma can improve oxygenation, reduce respiratory effort, and diminish the need for intubation; decrease hospital stay and PICU stay if applied early on.

Conflict of Interest: None

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