Original Research Paper Pediatrics

Efficacy of Hypertonic Saline Along with Salbutamol in Acute Wheezing in Children Aged 2—6 Years Attending a Tertiary Care Hospital

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KEYWORDS

INTRODUCTION

DEFINITION:

Wheeze is defined as a musical sound which is continuous and originates from oscillations in narrowed airways.

Polyphonic wheezing occurs due to widespread narrowing of airways that leads to various pitches, which is typically seen in bronchial asthma. The airflow obstruction in airways is affected by the airway caliber and compliance of the lung.

Airway resistance in the tube is inversely related to the radius of the tube to the fourth power. In most of the children aged less than 5 years of age, the small diameter of the peripheral airways can lead to 50% of airway resistance. In these children, an acute viral infection leads to increased mucous secretion, inflammation and associated broncho constriction leads to acute wheezing episodes.

The viral induced upper and lower respiratory tract infections are the most common cause for acute wheezing episodes and admission in hospital and development of asthma in later age. The most common pathogens are Human rhino virus, Respiratory syncytial virus, Human metapneumo virus (HMPV), Human Para influenza virus (HPIV), Entero virus(EV), Influenza virus(INFV), Adeno viruses and HumanBoca viruses. In the above viruses Human rhino virus, respiratory syncytial virus, Human Para influenza viruses are most commonly responsible for inducing acute wheezing episodes in children.

In recent studies it has been revealed that rhino viruses in the lower respiratory tract causes fluid and electrolyte movement across the luminal surface of the epithelial cells of the respiratory tract. These rhino viral infections increase the extra cellular adenosine tri phosphatase levels, which in turn leads to decrease in extra cellular adenosine tri phosphate levels which in turn leads to decrease in chloride secretion and increase in the levels of sodium absorptions from airway surface liquid.

Water is transported from airway surface liquid in to the mucosa along with electrolytes. This in turn leads to dehydration of airway surface liquid and edema of sub mucosa and adventitia. These viral infections also cause increased mucous secretions and epithelial sloughing. They also lead to mucous plug formation. From above details it is clear that these viral infections by causing airway surface liquid dehydration cause failure of mucous clearance.[2]

AIRWAY SURFACE LIQUID

The airway surface liquid is a thin layer of fluid, which covers the lumen of airways has a protective role of the airway epithelial cells from dehydration and inhaled particles, pathogenic organisms like bacteria and viruses.

The airway surface liquid has two layers[3]

1. Gel or mucous layer which floats over sol layer.
2. Watery periciliary or sol layer.

The exact volume and composition of these layers are still correctly not known.

The airway surface liquid is regulated by two ionic transport processes across airway epithelium.

These two transport mechanisms are:[4]

1.Sodium absorption.

2.Chloride secretion.

So the proper function of airway surface liquid is necessary for optimal function of mucociliary clearance, this in turn prevents retention of mucous and inhaled particles either organic or inorganic. Defective mucociliary clearances are the main predisposing factors for the pathogenesis of a number of chronic respiratory problems. There are number of therapies aimed at removing these accumulated mucous from airways.

Chest physiotherapy is an example of physical removal of these retained secretions. It is highly effective, but expensive and time consuming. Pharmacotherapy which aims to enhance mucociliary clearance from airways includes mainly two agents, nebulized hypertonic saline, nebulized mannitol. Inhalation of six percent hypertonic saline with 10ml volume has dramatically improved symptoms of patients with cystic fibrosis.[5]

Also the mannitol when given as aerosol from nebulizer improved the mucociliary clearance in cystic fibrosis patients and bronchiectasis.

MECHANISM OF ACTION:

Classification of muco active agents,[6,7,8]

- Mucolytic
- Expectorants
- Mucokinetics
- Ion transport modifiers
- Other muco regulatory agents.

As far as hypertonic saline is concerned it cannot be fitted into the group of muco active agents because of multiple mechanisms of actions. Mucolytic agents disintegrate the structure of mucus and decrease its viscosity and elasticity. So the main aim of any mucolytic agent is to decrease the viscoelasticity of the airway secretions to facilitate their clearance from the airways.[9]

Even though hypertonic saline is not a mucolytic agent it is capable of disintegrating the ionic bonds within the mucous gel and decreasing cross linkage entanglements. Hypertonic saline disintegrates the DNA from the mucoprotein, which in turn allows the natural proteolytic enzymes to digest the mucoprotein.[10]

Hypertonic saline markedly increases the depth of liquid layer in the airway surface liquid by attaching to it. Hypertonic saline being an osmotic agent draws liquid into airway surface liquid from epithelial cells. Degree of restoration of the airway surface liquid varies depending upon the dose of hypertonic saline given locally as nebulization. Hypertonic saline also triggers cough, which improves cough mediated clearance.

Recently hypertonic saline appears to increase the level of two thiols[3]

- Glutathione
- Thiocyanate

Present in the airway surface liquid which has a protective effect against oxidation injury, which causes airway inflammation and release of neutrophils, eosinophil , mast cells, basophils and pro inflammatory mediators which in turn leads to edema, decreased mucociliary clearance, increased mucous production and chronic obstructive airway disease.

ACUTE WHEEZING IN 2-6 YEARS OLD

There are several phenotypes involved in recurrent preschool wheezing and it has variable prognoses and management.

Recurrent preschool wheezing is not synonymous with asthma because of its obvious relation to viral illness, temporal nature and lack of data on underlying inflammatory process.

PHENOTYPES IN PRESCHOOL WHEEZING:-

Two Major phenotypes involved.

1. Virus induced wheezing.
2. Multi trigger wheezing.

VIRAL INDUCED WHEEZING:-

It accounts for about two- thirds of all preschool wheezing. These phenotypes have normal premorbid lung function, intermittent airway obstruction and are asymptomatic between each episode.

These children usually have a favorable prognosis. They only need supportive treatment.

Respiratory syncytial virus can produce severe respiratory distress below 2 years of age and may lead to recurrent wheezing episodes in preschool children.

Human meta pneumovirus can also produce recurrent wheezing episodes.

It has been proved that Rhinoviruses can trigger wheezing in early life and may lead to asthma in later life.

MULTITRIGGER WHEEZING:-

It is less common in early years of life, as it is usually caused by allergy. It manifests in preschool years of life.

Family history of asthma and allergy is present with this phenotype. It usually persists beyond early childhood. It is associated with significant deficits in lung function and growth up to 11 years of age.

EUROPEAN RESPIRATORY SOCIETY TASK FORCE APPROACH TO PRESCHOOL WHEEZING:-

1. Preschool wheezing is classified in to episodic (viral) induced wheezing or multitrigger wheezing.
2. The terms used, such as transient, late onset and persistent wheeze should be limited to population – based cohort studies only.
3. In preschool wheezing the term "ASTHMA" should not be used because of lack of evidence of underlying inflammation.

APPROACH TO THE ASSASSMENT OF PRESCHOOL WHEEZING BY EUROPEAN RESEARCH SOCIETY:-

- In history taking personal history, family history of allergies, pattern and trigger of wheeze and house hold smoking should be assessed.
- In children requiring long term management allergy testing should be performed.
- Health care professional should verify when a parent reports wheezing to their child.
- Further investigations are needed only in severe, therapy resistant or wheezing associated with clinical features.

PHARMACOLOGICAL THERAPY

For the prevention of symptoms and improvement of long term outcome of preschool wheezing, along with allergen avoidance, parent education, environmental control, pharmacological treatment plays an important role.

ACUTE MANAGEMENT:-

Acute preschool wheezing symptoms are treated with

1. Oxygen
2. Short acting beta-agonists
3. Systemic corticosteroids(prednisolone)

In mild to moderate wheezing due to viral infections oral prednisolone has not been much useful.

The usefulness of ipratropium bromide is minimal. It may have additional effect to short acting beta-agonists,

NEBULIZER

A Nebulizer is a device which changes liquid medication into a mist which can be easily inhaled into the respiratory system for the delivery of aerosolized drugs.

AEROSOL DEPOSITION:

The efficacy of an aerosol as a vehicle for delivering drugs in to the lower airways depends mainly on droplet or particle size. Smaller particles have greater chance of peripheral penetration and retention.

The particles with size of more than 10micro meter in diameter are most likely to deposit in the mouth and throat. Particles with size between 5 to 10 micrometers in diameter are deposited in upper airways.

Particles with size less than 5 micrometer in diameter are deposited frequently in the lower airways which are most appropriate for pharmaceutical aerosols.

DRUGS THAT CAN BE DELIVERED THROUGH NEBULIZATION.

Salbutamol, corticosteroids, ipratropium, adrenaline, hypertonic saline, normal saline can be delivered through nebulizers. Drugs are available as respules or vials. When vials are used drug was to be diluted with saline and not with plain water.

POTENTIAL HAZARDS OF NEBULIZATION:-

Salbutamol Nebulization without oxygen in a sick child with wheeze can cause preferential bronchodilatation resulting in ventilation perfusion mismatch and lead to deterioration in clinical condition of the child. Hence nebulization should always be given with oxygen in a sick child.

An alternative to using Jet nebulizer is connecting nebulization chamber to oxygen humidifier and using oxygen driven nebulization. Oxygen delivered at rates of 8-10 liters per minute, break the drug solution into mist and results in effective nebulization.

CLINICAL SEVERITY SCORE

Respiratory Rate	1 Point	2 Point	3 Point
2-3 Years	< 34	35-39	> 40
4-6 Years	< 30	31-35	> 36
Oxygen Saturation in room air	> 95	90-95	< 90
Auscultation	Normal or End Expiratory wheezing	Expiratory wheezing	Inspiratory & Expiratory wheezing / decreased breath sounds or both

Retractions	None / Intercostal retractions	Inter costal & Substernal retractions	Inter costal / Sub costal & Supraclavicular retractions
Dyspnea	Speaks in sentences	Speaks in short sentences	Speaks in single words / Grunts
CS Score	5-7 (Mild)	8-11 (Moderate)	12-15 (Severe)

REVIEW OF LITERATURE

Dorit ater et al,conducted a study on hypertonic saline with albuterol in preschool children with acute wheezing episodes. It was a prospective randomized double blind study. In this study children aged between 1 to 6 years attending emergency department are evaluated for the efficacy of 5% hypertonic saline with albuterol was compared with 0.9 % normal saline with 0.5ml albuterol. A sample size was 41. These children was given 1 dose of albuterol inhalation. Then they are given 4ml of 5% hypertonic saline with 0.5ml of albuterol or 4ml of 0.9% normal saline 2 doses with 20 minutes interval four times a day if they are admitted in the hospital.

In this study the primary outcome measured was length of hospital stay. The secondary outcome measured was clinical severity score and admission rate. In 5% hypertonic saline group 16 children were involved and in 0.9% normal saline group 25 children were involved. In this study length of stay was significantly lower in hypertonic saline group than normal saline group. Median 2 days (range 0 to 6) against 3 days(range 0 to 5)days. P value 0.027.

Admission rate was significantly lower in hypertonic saline group in comparison with normal saline group. The admission rate was 62.2% in hypertonic saline group, against 92% in normal saline group. The clinical severity score significantly improved in both groups. But there is no significant correlation between them.

Mark R Elkins et al conducted a study of mechanism of action of hypertonic saline in cystic fibrosis patients. They found out that inhalation of various concentration of hypertonic saline increased the ability of the patients to expectorate the mucous from the respiratory tract.

Reider and Colleagues conducted a cross sectional study in persons with cystic fibrosis disease exacerbation. In this study persons are divided in to two groups: normal saline group and hypertonic saline (6%) group. Prier to the physiotherapy they were given nebulization with 0.9% and 6%. Hypertonic saline and 1 hour after sputum is collected from these patients with physiotherapy. Sputum expectoration was more in hypertonic saline group than in normal saline group.

E. Michael sarrel and Colleagues conducted a study in ambulatory children with viral bronchiolitis with 3% hypertonic saline nebulization. They had found out that 3% hypertonic saline along with terbutaline has effectively decreased the symptoms of bronchiolitis in these children.

Avigdor Mandelberg and Colleagues conducted a study in infants with viral bronchiolitis along with Epinephrine 1.5mg. 4ml of 0.9 % and 3% hypertonic saline. They found out that 3% hypertonic saline along with 1.5mg of epinephrine inhalation had decreased the length if signs and symptoms in comparison with 0.9% saline along with 1.5mg of epinephrine.

Suri et al conducted a study on the effect of hypertonic saline and durnase – alpha on the inflammatory mediators in cystic fibrosis. They have found out that after 3% hypertonic saline inhalation the Interleukin levels are significantly reduced.

STUDY JUSTIFICATION

Most of acute wheezing episodes requiring hospitalization are caused by viruses.

A therapy which maintains Airway hydration, promoting mucous clearance and reducing sub mucosal edema are required for reducing, admission rate, morbidity and length of stay. The studies which were done previously included children with bronchiolitis. There are no studies on Indian context, since seasonal variation is different from country to country. This study will be done in children between 2to 6years by excluding bronchiolitis. In a country like India this therapy if proven will be cost effective and feasible.

OBJECTIVEOF THE STUDY

To compare the efficacy of hypertonic saline and normal saline as a vehicle for salbutamol Nebulization in acute wheezing attacks in children aged 2 to 6 years attending a tertiary care hospital.

METHODOLOGY

STUDY DESIGN:-

Clinical trial (Quasi experimental design).

STUDY SETTING:-

CASUALTY OF INSTITUTE OF CHILD HEALTH, EGMORE, CHENNAI.

STUDY PERIOD:-

March 2014 to September 2014.

TIMELINE:-

- DATA COLLECTION: March 2014 to July 2014.
- DATA ANALYSIS AND MANUSCRIPT PREPARATION: AUGUST 2014.
- SUBMISSION OF REPORT: September 2014.

STUDY POPULATION:

INCLUSION CRITERRIA:-

All children aged 2-6 years with acute wheezing attacks with clinical severity score of > 8.

EXCLUSION CRITERIA:-

1. Children with cardiac disease.
2. Children with chronic renal disease.
3. Children requiring ICU admission.

SAMPLE SIZE:-

100.

SAMPLE SIZE CALCULATION:-

Assuming an effect size of 0.25(from previous studies) with α error of 5% and power of 80% sample size of 50 in each group was arrived.

DEFINITIONS USED:-

CASES:-

Children who receive 3% hypertonic saline Nebulization along with salbutamol are called cases or treatment group.

CONTROLS:-

Children who receive 0.9% normal Saline Nebulization along with salbutamol are control group.

ADMISSION CRITERIA:-

Asthma clinical severity score of >6.

PARAMETERS USED:-

1. Respiratory rate.
2. Auscultation.
3. SPO2.
4. Speech.
5. Subcostal retractions.

Each parameter scored as 1, 2, and 3.

Total score categorized as mild(5 to 7), moderate(8 to 11) and severe(12 to 15).

OUTCOME MEASURED:-

1. Admission rate
2. Clinical severity score <6

STUDY MANOUVERE

The children were enrolled on the basis of inclusion criteria after obtaining written informed consent from either of parent.

Base line demographic data and clinical history were noted in standard format. A baseline clinical severity score was obtained based on clinical examination at the start of the study.

DESCRIPTION OF VARIABLES:-

Respiratory rate:-

Respiratory rate was counted for a full one minute. Before counting respiratory rate child was kept in mothers lap in upright position to decrease anxiety. The clothes of upper part of the body were removed before counting respiratory rate. Using a watch with seconds hand respiratory rate was counted by inspection for a full 60 seconds. One chest rise and fall were counted as one breath.

While counting respiratory rate attention of the child was diverted to prevent anxiety.

Oxygen saturation:-

Oxygen saturation was measured with a help of Nelcor pulse oximeter. Probe of the pulse oximeter was put over the child's finger or toes which are not nail polished.

Auscultation:-

Before auscultation child's clothes on the upper part of the body was removed and was kept on mothers lap. Child's attention was diverted and auscultated with the diaphragm of the stethoscope in all auscultatory areas (supraclavicular, infra clavicular, axillary, infra axillary, supra scapular, infra scapular, inter scapular areas) for adventitious sounds.

Speech:-

Child was asked some questions and its speech pattern was noted. Whether child was able to speak in full sentence or in short sentence or in single words was noted.

Work of breathing:-

Work of breathing was noted by undressing the child's upper part of the body and looking for intercostal, subcostal and supraclavicular retractions.

STATISTICAL ANALYSIS

Data was entered in excel sheet. Statistical analysis was done using statistical software SPSS. Qualitative variable were expressed as proportion and quantitative variables as mean and standard deviation. Outcome variable was described as risk difference with 95% confidence interval.

ETHICAL CONSIDERATIONS

- Ethical clearance from institutional review board was obtained.
- Written informed consent was obtained from parent of each patient.
- Strict confidentiality of data was maintained.

FLOW CHART

Out of 114 children assessed 14 were eliminated and 100 cases were analyzed.

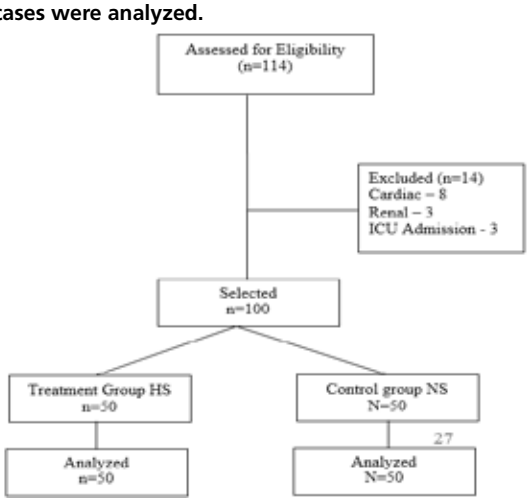


TABLE SHOWING FREQUENCY OF AGE IN STUDY POPULATION

Age in years	Frequency	Percent
3	28	28.0
4	45	45.0
5	13	13.0
6	6	6.0
Total	100	100.0

In this frequency table majority of the children were (45) in 4 years of age.

TABLE SHOWING FREQUENCY OF SEX DISTRIBUTION

Sex	Frequency	Percent
Male	61	61.0
Female	39	39.0
Total	100	100.0

In this study 61% were males and 39% were females.

TABLE SHOWING H/O ASTHMA IN FAMILY

Family History of Asthma		Frequency	Percent
	Present	50	50.0
	Absent	50	50.0
	Total	100	100.0

50% had family history of Asthma and 50% had none.

FREQUENCY TABLE SHOWING HISTORY OF PREVIOUS NEBULIZATION IN STUDY GROUP

H/O Previous Nebulization	Frequency	Percent
Yes	66	66.0
No	34	34.0
Total	100	100.0

66% had previous Nebulization and 34% had no history of previous Nebulization.

Frequency table work of breathing in study population

Work of Breathing	Frequency	Percent
None	3	3.0
Intercostal / Sub sternal	49	49.0
Intercostal and supraclavicular	48	48.0
Total	100	100.0

Out of 100 children 49 had inter costal or sub sternal retractions, 48 had intercostal and supraclavicular retractions, 3 had none.

Frequency of breath Sounds in study population

Breath Sounds	Frequency	Percent
Normal/End Expiratory wheezing	2	2.0
Expiratory wheezing	10	10.0
Inspiratory and Expiratory	88	88.0
Total	100	100.0

88% of children had inspiratory & expiratory wheezing, 10% had expiratory wheezing and 2% had normal or end expiratory wheezing.

Frequency table showing oxygen saturation in study population

SPO2 in %		Frequency	Percent
	>95	5	5.0
	90-95	95	95.0
	Total	100	100.0

Out of 100 children 95% had oxygen saturation of 90 to 95% and 5% had oxygen saturation of> 5%.

Frequency table showing base line Score in study population

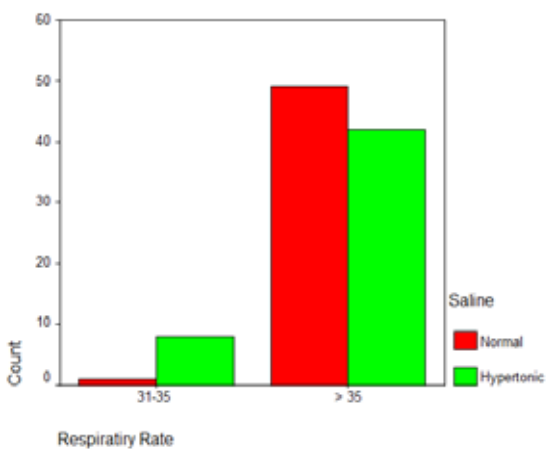
Base line Score		Frequency	Percent
	Moderate	19	19.0
	Severe	81	81.0
	Total	100	100.0

81 % of children had severe base line score and 19 % had moderate base line score.

Adverse effects

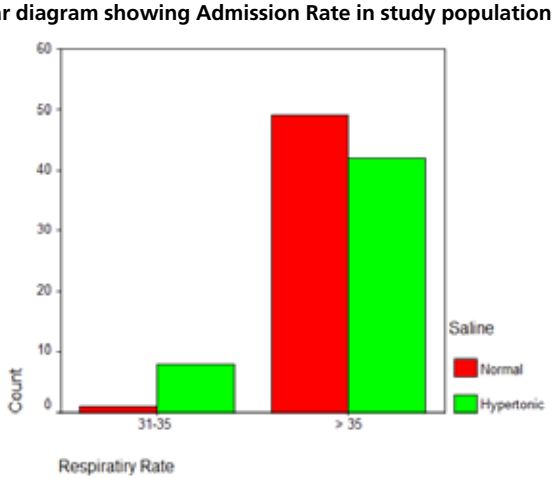
Out of 100 children none of them had developed any adverse effects during the study.

Bar diagram showing respiratory rate in this study population



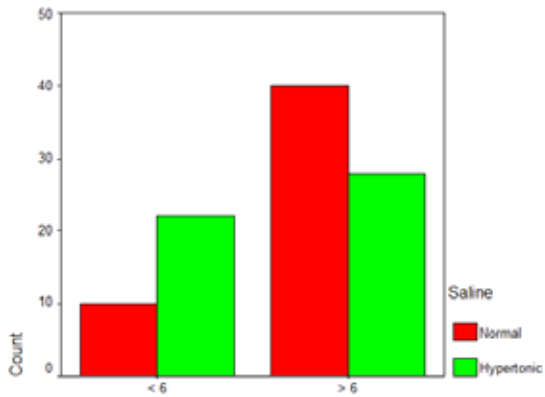
P value is 0.014 and it is significant.

Bar diagram showing Admission Rate in study population



P value is 0.009 and it is significant.

Bar diagram showing Clinical Severity Score in study population



P value is 0.010 and it is significant.

DISCUSSION

The study was done on 100 patients with 50 in Hyper tonic saline group and 50 in Normal saline group.

The mean (50) age was 3.81(0.97) with maximum patients (45%) of age 4. Sex ratio was 61:39 with male preponderance. Half of the patients had positive family history while 66% were nebulized in past.

91% had respiratory rate more than 35 while 9% had respiratory rate between31-35. 48% had intercostal and supraclavicular retractions while 49% had intercostal and sub sternal retractions and only 3% had no retractions. 88% had wheezing heard in both phases of respiration while 10% had only expiratory wheezing and 2% had just end-expiratory wheezing. 95% had oxygen saturation between 90 to 95% while only 5% had between above 95%. All of them were able to speak in short sentences. Overall as per baseline score 0.81% had severe respiratory distress and 19% had moderate respiratory distress.

Out of 100 patients, 70 were admitted, admission rate being 70%. Post nebulization clinical severity score was <6 in 32%. None of patients were noted to have any adverse events in either of group.

Both groups were comparable in terms of baseline parameters like ages sex, family history of asthma and previous history of nebulisations. Normal saline group had more number of patients with respiratory rate >35 than the hypertonic saline group. But, other variables of scoring like work of breathing, oxygen saturation auscultatory findings and speech were comparable in both the groups. The overall baseline clinical severity scoring was comparable in both treatment groups.

The admission rate in hypertonic saline group (58%) was less than that in normal saline group (82%) and the difference was statistically significant (p-0.009). The risk difference was 24% and its 95% confidence interval was (6 to 40%).

Post nebulization clinical severity score less than 6 was found in 20% in normal saline group and 44% in hypertonic saline group which was also statistically significant (p=0.01). Thus more patients improved after hypertonic saline nebulization compared to normal saline nebulization.

Thus our study clearly indicates that hypertonic saline is superior to normal saline as a vehicle for salbutamol nebulization in preschool children with acute wheezing.

This is in concordance with study done by Dorit Ater at al which reported a 30% reduction in admission rate following hypertonic saline as compared to normal saline nebulization.

Though hypertonic saline is not a mucolytic per se, it is capable of disintegrating ionic bonds within mucous gel and decreasing cross linkages and thus improves mucus clearance. Thus hypertonic saline is superior to normal saline in causing resolution of clinical symptoms.

LIMITATIONS

In our study, the respiratory rate in baseline clinical severity scoring was not comparable and had statistically significant difference between both treatment groups with severe patients in normal saline group.

However no such difference was observed in other variables of score as well as overall score making both the groups comparable.

Randomization was not done and alternate patients were allotted to either group. But this did not result in significant bias as most baseline parameters were comparable in both groups.

Blinding was not done which could have resulted in observer bias.

Past and present history of oral medications was not taken into considerations for analysis. This could have an effect on outcome measured.

RECOMMENDATIOINS:-

Hypertonic saline can be preferred over normal saline as vehicle saltbutamol nebulization in preschool wheezes.

Further double blinded randomized control trial taking drug history into considerations to be done to prove the superiority of hypertonic saline over normal saline.

CONCLUSION

Hypertonic saline is superior to normal saline as a vehicle for salbutamol nebulization in decreasing admission rate and improving asthma severity score.