

THE EFFICIENCY OF NEBULIZED SALBUTAMOL MONOTHERAPY AS COMPARED TO COMBINATION THERAPY WITH IPRATROPIUM BROMIDE IN ACUTE SEVERE ASTHMA AMONG CHILDREN

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Abstract

Introduction: asthma is a prevalent disease among pediatric population and about 300 million people is affected globally. Although there is many drugs available, suggestion and clinical trials of different drugs and combined regimens are continuously making the management more efficient than before. Short Acting Beta Agonists (SABA) is the ones which are used frequently and muscarinic acetylcholine antagonist ipratropium bromide (IB) are also on the line. The use of SABAs are usually done as single regimen but suggestions have been done that combining with IB may result in efficient outcome. This current study explored the efficiency of Salbutamol monotherapy with that of combined regimen with IB and expressed the efficiency in terms of Peak Expiratory Flow Rate measured using spirometer.

Methods: The study was conducted from March, 2021 to November 2021. The study design is prospective cohort and included 127 pediatric patients. The pediatric patients were considered who had confirmed asthma. The study considered Peak Expiratory Flow Rate (PEFR) as the determinant of the study outcome. PEFR was measured using spirometer. The patients were divided into 2 groups, group 1 received salbutamol monotherapy while group 2 received ipratropium bromide along with salbutamol. Then the PEFR at the starting of the treatment was measured and after the receiving the monotherapy or the combination, PEFR was measured at fixed interval. The rise of PEFR was plotted against a chart with time in X-axis.

Result: it was found that the group 2 patients who received a combination therapy of salbutamol and ipratropium bromide have responded more efficiently as compared to the patients of group 1.

Conclusion: the authors considered that the combination of salbutamol and ipratropium bromide is more efficacious in managing acute moderate to severe asthma among the pediatric population.

Keywords: asthma, salbutamol, ipratropium bromide, pefr.

Introduction

Asthma is a very notoriously known illness among children and is assessed to influence 300 million people round the globe^[1]. In China, asthma influences 3% of youngsters ≤ 14 years old and the occurrence of asthma in toddlers has expanded by almost 50% in the course of recent years^[2]. Asthma-related hospitalization can adversely influence the personal satisfaction of kids and their parental figures. Furthermore, medical services uses for asthma-related conditions force extensive financial weight on society^[3,4]. Acute severe asthma (ASA) in kids is the third most normal reason for clinic visit and one of the most normal reasons for Pediatric emergency unit admission^[5]. The universality of asthma is rising and the number of demises from asthma has been increasing increased^[6]. According to the US Center for Disease Control and Prevention (CDC) Asthma Surveillance Survey, the incidences of asthma during 2001-2003 were assessed at 8.5% in kids, and the load of asthma has expanded over 75% from 1980-1999^[7,8]. Asthma is likewise a normal respiratory issue in Pakistan^[9] Up to 4% of children going to the out-patient ward in one review experienced bronchial asthma^[10].

Practically all accessible rules suggest that the rehashed organization of breathed in short-acting β_2 -agonists (SABAs, up to 4–10 puffs at regular intervals for the main hour) is a powerful and proficient method for accomplishing fast inversion of air way constraint in patients with asthma^[11]. According to the most recent rule^[12], SABA- only immediate treatment is not generally suggested for asthma in grown-ups or children because of its danger of asthma-related death and dire asthma-related medical care. Thus the new rules^[13] have suggested the expansion of ipratropium bromide (IB), a short-acting “muscarinic acetylcholine receptor antagonist”, to SABAs as a discretionary treatment for youngsters and teenagers with ASA. Despite the fact that IB doesn't appear to be extremely productive in controlling asthma, a few examinations have shown that a mix of IB and SABAs is related with less hospitalizations and more noteworthy improvement in “peak expiratory flow (PEF) and forced expiratory volume in one second (FEV₁)” contrasted with singular use of SABA in kids with ASA^[14,15]. It has been suggested that IB should be added to SABA in the initial first hour of treatment^[12] particularly in kids.

ASA is a hazardous health related crisis described by episodes of expanding hack, wheezing, chest downturn and powerlessness to talk or drink, which may cause complete breakdown of respiratory mechanism left overseen (in short span of time)^[16]. Normal triggers of ASA are viral diseases, allergens (cockroaches, dust-mites, dusts and molds), air contamination furthermore tobacco smoke^[17,18].

A nebulizer is a piece of clinical equipment that an individual with asthma or another respiratory condition that can be used to induce medicine straightforwardly and rapidly to the lungs. A nebulizer transforms fluid medication into an extremely fine mist that an individual can breathe in through a facial covering or mouthpiece. Ventolin is a brand name for a medication called salbutamol, which is a bronchodilator or reliever medication used to open up patient's air-passages. Salbutamol is called albuterol in the USA. Ventolin comes as two kinds of inhaler - the accuhaler and the evohaler^[19].

Salbutamol (SbL) are utilized to alleviate asthma indications. It works by loosening up the muscles of the air-ducts that lead into the lungs, which makes it simpler to relax. SbL arrives in an inhaler (puffer). SbL inhalers are normally blue. SbL can be in some cases given as tablets, or syrup for individuals who can't utilize an inhaler (for any/varied reasons). It can likewise be given utilizing a nebulizer, and is often used in cases of severe asthma. A nebulizer is a machine that assists with taking in the medication as a mist, utilizing a veil or a mouthpiece^[19]. SbL inhalers are secure and competent with rare incidental effects assuming that they are employed efficiently. They can be classified as tow-"reliever" inhalers since they give speedy alleviation from breathing issues when required; "preventer" inhaler to help stop (forestall) side effects and which are used in routine basis. Use of SbL inhalers more than 3 times each week, must be taken seriously and reported to concerned clinician. Most grown-ups and children, everything being equal, can utilize SbL inhalers. Salbutamol is safe for most individuals (some exceptions may be there)^[20].

For people who lack ease in using a nebulizer an added attachment called spacer can be provided a spacer is an enormous metal or plastic holder with a mouthpiece and an opening for the inhaler. When utilized with the inhaler it makes it more straightforward to get the perfect measure of salbutamol into the lungs. These are particularly valuable for giving salbutamol to little children. One common side effect of using a nebulizer is fast pace of heart beats making the patient feel unsteady but they are not considered hazardous, as long as not accompanied by chest pain. They normally disappear inside 30 minutes or a couple of hours all things considered^[21].

Epidemiology

There is a huge geological variety in asthma predominance, seriousness, and mortality. While asthma predominance is gigantic in high-income nations, most asthma-related mortality happens in low-medium pay nations^[22]. Patterns of asthma rate and pervasiveness contrast among children and grown-ups. It is notable that asthma frequently starts in childhood however can happen all through life. While asthma frequency and commonness is higher in kids, asthma-related medical services use, and mortality are higher in adults.

Now the modern researchers consider "asthma" as an umbrella term that means encompassing numerous diseases having analogous clinical manifestations yet differing in core pathophysiological conditions^[23], commonly called by the name "asthma endotypes"^[22].

To better understand, absorb and study severe childhood asthma a yet another calling coined by Bush et al. is known as "Problematic severe asthma" (PSA) that covers those kids who fail to pass asthma treatment and thus command specialist referral^[24]. Such cases after asthma-like symptoms get expelled are further divided into 3 distinct (sometimes intersecting) groups: "Difficult-to-treat asthma; Asthma with co-morbidities (Asthma plus); and Severe therapy-resistant asthma"^[24].

Essentially, RCT's of pediatric asthma (PdA) intensification and a meta-examination of PdA patients recommend that ipratropium bromide (IB) added to beta-2-agonists further helps lungs to function better additionally diminishing incidences to get hospital admission in ASA. No extremities were reported indeed there could be seen modicum excellence regarding the statistics of air flow obstruction when IB was deployed in combination with B₂Ag. Likewise IB has shown to improve clinical aftermath in kids suffering from acute asthma. The study recommended this dual-mix as it was effective minus any hostile upshots^[25].

Methods

The study has been conducted from March 2021 to November 2021. The study design is a prospective cohort study and included 127 pediatric patients. The patients who were in the pediatric age group and their treatment was done in the institution were only considered. The patients who did not continue their treatment in our institution were not considered. The included patients were of confirmed asthma of moderate to severe severity, which is classified based on the status of Peak Expiratory Flow Rate (PEFR). The criteria of PEFR for the pediatric population is given below^[26]. PEFR was measured by spirometry.

	Mild to Moderate	Severe	Life threatening
PEFR	> 50% to 75%	33% to 50%	< 33%

The study has divided all the patients randomly into 2 groups, namely, group 1 (n=64) who received nebulised salbutamol at a dosage of 0.03 ml/kg and group 2 (n=63) who received a regimen of combined salbutamol (previous dose) with Ipratropium bromide (3 doses) at a dose of 250 mcg/dose. In both the groups, the patients received the mentioned drugs at 20 minutes intervals and were under

observation. PEFR was noted down at 30 minutes, 60 minutes, 120 minutes and 180 minutes.

Results

The study included 127 pediatric patients ranging from 4 years old to 13 years old, with a mean of 8.53 ± 2.77 years old. The number of male patients was 51 while the number of females was 69.

Table 1: The number of patients in each group before the treatment

PEFR	Group 1	Mean PEFR	Group 2	Mean PEFR
Mild to Moderate (> 50% to 75%)	39	62	35	64
Severe (33% to 50%)	25	42	28	43

After receiving the above mentioned drugs at mentioned doses, the same patients were monitored at particular intervals.

The findings of PEFR at fixed intervals in the patients of group 1 are presented below (Table 2). It has been shown

that the number of patients increased from 0 to 18 in 30 minutes post nebulised salbutamol therapy followed by 31, 43 and 52 at 60 minutes, 120 minutes and 180 minutes, respectively.

Table 2: The summary of PEFR at fixed intervals in Group 1 (n=64) patients after receiving mentioned drug

PEFR grade	PEFR ₀	PEFR ₃₀	PEFR ₆₀	PEFR ₁₂₀	PEFR ₁₈₀
More than 75%	0	18	31	43	51
Mild to Moderate (> 50% to 75%)	39	28	23	15	13
Severe (33% to 50%)	25	18	10	6	0

Similarly, PEFR was recorded at fixed intervals in group 2 patients. The findings of PEFR at fixed intervals are presented below (Table 3). It has been shown that the number of patients increased from 0 to 22 in 30 minutes post combined drug therapy followed by 35, 49 and 59 at 60 minutes, 120 minutes and 180 minutes, respectively.

Table 3: The summary of PEFR at fixed intervals in Group 2 (n=63) patients after receiving mentioned drug

PEFR grade	PEFR ₀	PEFR ₃₀	PEFR ₆₀	PEFR ₁₂₀	PEFR ₁₈₀
More than 75%	0	22	35	49	59
Mild to Moderate (> 50% to 75%)	35	27	21	13	4
Severe (33% to 50%)	28	14	7	1	0

The outcome of the monotherapy (group 1) and combined therapy (group 2) was determined by the finding of PEFR (which should be more than 75% to consider as efficient) at fixed intervals. The comparison of the PEFR among group 1 and group 2 patients was charted against each other with respect to time (Figure 1).

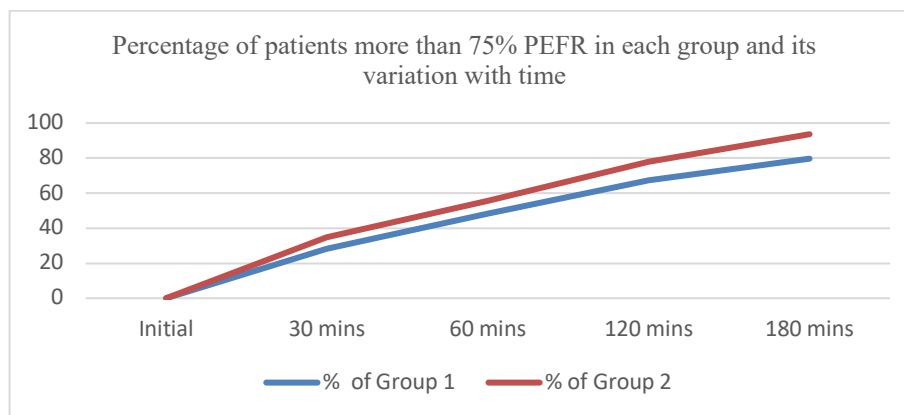


Figure 1: The Percentage of patients more than 75% PEFR in each group and its variation with time

Discussion

In the present study, Figure 1 showed that group 2 patients who received a combination therapy of salbutamol and ipratropium bromide have responded more efficiently as compared to the patients of group 1. The efficiency was determined by measuring Peak Expiratory Flow Rate (PEFR) using spirometer which is a considerable indicator for oxygenation to the lungs^[26].

A random, double-blind investigative study on children was undertaken by **Iramain, R. et al (2011)**^[27] to unveil if salbutamol in addition to ipratropium bromide further develops oxygenation and lung work and lessens the recurrence of hospitalization in kids with asthma emergencies. Evaluation of patients was done utilizing the asthma score and spirometry. They got six nebulizations of salbutamol in addition to placebo treatment or salbutamol in addition to ipratropium and were reconsidered at 30, 60, 90, 120, and 240 minutes, which was the decision making time if they needed hospital admission or not. There were 97 patients in total where 49 received salbutamol in addition to ipratropium and 48 were on salbutamol monotherapy. Results revealed that initially both groups did not showed any noticeable differences but later kids treated with salbutamol in addition to ipratropium exhibited a more noteworthy improvement in clinical state and lung work and required hospitalization in lesser frequency (18.4%) than those with only salbutamol (43.8%) ($p = .007$). This degree of improvement was more prominent in youngsters with serious asthma emergencies than in those with moderate emergencies. The impact of salbutamol in addition to ipratropium was much similar in kids less than of 8 years of age and also in older kids^[27].

A secondary study led by **Rodrigo & Castro-Rodriguez (2005)**^[15] tried to validate that is utilization of a blend of inhaled β_2 agonists and anticholinergics, superior to solitary use of β_2 agonists in patients with intense serious or perilous asthma crisis. A pursuit was directed of all randomized controlled trials (RCT) that got on print before April 2005. Results revealed that data gathered from 32 RCT's ($n=3611$ subjects) showed slump in medical clinic admission of children who got treated with inhaled anticholinergic combo ($RR=0.73$; 95% CI 0.63 to 0.85, $p=0.0001$). The same treatment likewise delivered a huge upsurge in spirometric boundaries 60–120 minutes after the last treatment ($SMD=-0.54$; 95% CI -0.28 to -0.81 , $p=0.0001$)^[15].

A recent study was undertaken by **Xu, H. et al (2021)**^[28] to assess the adequacy and wellbeing of IB + salbutamol in the treatment of asthma in kids. It was a secondary study that involved most studies published based on random control trials till Sept. 2020. The studies incorporated children and either dual-treatment of IB + salbutamol or mono-therapy with only salbutamol. The primary results included chances of hospitalization and adverse occasions.

The study utilized “random effects model” with a 95% confidence interval. Out of the total 1061 studies that could be identified, 55 were included (as they fulfilled all parameters of inclusion) and total number of participants was 6396. Results revealed that combination treatment (IB + salbutamol) effectively suppressed chances of hospitalization when contrasted with salbutamol monotherapy (“risk ratio [RR] 0.79; 95% CI 0.66–0.95; $p = 0.01$; $I^2 = 40\%$ ”)^[28].

A study undertaken in Bangladesh by **Hossain, A. S. et al (2013)**^[29] compared respiratory treatment of children suffering from acute severe asthma. Patients were distributed into two groups: first *control group* receiving Salbutamol mono therapy and second was *case group* that was on dual-drug therapy (Salbutamol + Ipratropium bromide). A jet nebulizer was employed to give 3-3 doses with a time gap of 20 minutes. Results revealed that peak flow was regularly monitored and it showed no difference at baseline but at 30 min. it was more in case group ($60.01 \pm 35.01\%$) as compared to Salbutamol group ($44.47 \pm 25.03\%$) and the difference was of 16% ($p=0.025$); at 60 min. it further improved. Thus it can be concluded that nebulized combo-treatment presented better bronchodilating result than solitary use of Salbutamol in cases of acute severe asthma^[29].

A recent comparative study in Multan region by **Joiya, S. J. et al (2020)**^[30] constituted of 104 asthmatic kids, 52 in each group. Group A was given only salbutamol alone and its counteractive group B was subjected to combination of salbutamol with Ipratropium bromide. Both groups also received O_2 via nasal prongs. Various criteria that were compared were “mean heart rate, respiratory rate, accessory muscle score, peak expiratory flow rate (PERF) percentage and SPO_2 ”. Results displayed that administration of combination of two drugs with the help of a nebulizer proved a better course of medication for children suffering from acute severe asthma. This was found to be quite safe, workably efficient and unswerving as null negative incidences were encountered thus the authors highly recommend combination therapy over salbutamol mono therapy in treatment of severe asthma in toddlers^[30].

Conclusion

The study has concluded that although both the groups responded well, group 2 which received combination drugs of salbutamol with ipratropium bromide showed significant improvement in PEFR as compared to the group which received salbutamol as single regimen. Therefore, it can be considered that the combination of salbutamol and ipratropium bromide is more efficacious in managing acute moderate to severe asthma among the pediatric population. However, the current study suggests to conduct more meta analysis of multicentre study involving comparison of

monotherapy and combination therapy in managing asthma.

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