A Comparative Study of Salbutamol Nebulizer versus Ipratropium Bromide plus Salbutamol Nebulizer in the Treatment of Children with Acute Asthma Exacerbation

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Abstract

Background: Patients with asthma may develop acute attack due to different types of triggering factors. Early recognition of an acute asthma exacerbation is crucial for effective management.

Objectives: To evaluate the effects of salbutamol nebulizer versus salbutamol plus ipratropium bromide nebulizer in children with acute asthma exacerbation attack.

Patients and methods: A randomized double blind standard control clinical study was conducted in Karbala Teaching Hospital for Children from 1st of November 2015 to the end of November 2016 on patients presented to the emergency room (ER) of the Hospital. The study was conducted on hundred patients presented with mild to moderate acute attacks of asthma, assigned to take either nebulized salbutamol or combination of salbutamol plus ipratropium bromide during their stay. Assessment of asthma severity was done for each patient according to pulmonary index score (PIS)

Results: There was significant reduction ($p < 0.05$) in PIS for patients treated with salbutamol alone and patients treated with combination therapy (ipratropium + salbutamol) after 30,60 and 90 minutes from ER admission as compare with their scores at baseline, 30 and 60 minutes respectively. After 30 minutes from ER admission, patients who were treated with combination of ipratropium bromide + salbutamol had significantly ($p < 0.05$) lower PIS (5.60 ± 2.77) than those treated with salbutamol alone ($PIS = 7.32 \pm 2.18$). The mean duration of stay in ER was

significantly ($p < 0.05$) shorter in patient treated with combination therapy (57.60±21.71 min) than those with salbutamol alone (77.40±16.13 min).

Conclusion: Treatment of asthmatic children with mild to moderate acute exacerbation attack with combination therapy of (ipratropium plus salbutamol nebulizer) improved the clinical condition, lowered pulmonary index score, and significantly shortened the duration of stay in emergency room as compared with salbutamol nebulizer alone.

Key wards: Ipratropium Bromide, Salbutamol, Childhood asthma, Acute Asthma Exacerbation

مقارنة تأثير تبخير السالبيوتامول مع تأثيرتبخير مزيج (الابراتروبيوم بروماید والسالبيوتامول) في علاج الأطفال المصابين بنوبة الربو الحادة

الخلفية:

المرضى المصابون بالربو من الممكن ان يتعرضوا لنوبة حادة بسبب أنواع مختلفة من المحفزات. ان التعرف المبكر على تفاقم الربو الحاد هو امر مهم لعلاج فعال.

الهدف:

لمقارنة تأثير تبخير دواء السالبيوتامول مقابل تأثير تبخير مزيج (الابراتروبيام والسالبيوتامول) في الأطفال المصابين بنوبة تفاقم الربو الحادة.

طريقة العمل:

دراسة سريريه مجهولة لكل من الباحث والمريض اجريت في مستشفى كربلاء التعليمي للأطفال في محافظة كربلاء للفترة من الاول من تشرين الثاني ٢٠١٥ لغاية الثلاثون من شهر تشرين الثاني ٢٠١٦ للمرضى المراجعين لوحدة الطوارئ مع نوبة تفاقم الربو الحادة. الدراسة أجريت على مئة مريض وتم تقسيمهم الى مجموعتين، المرضى في المجموعة الاولى البالغ عددهم خمسون مريض اخذوا الدواء المزيج (تبخيرالابراتروبيام والسالبيوتامول) اما المرضى في المجموعة الثانية اخذوا دواء السالبيوتامول لوحده. وتم تقييم شدة النوبة وفق المؤشر التقييمي الرئوي (PIS) والذي يعتمد على الحالة السريرية للمريض وفق مؤشرات معينه.

النتائج :

كان هنالك تحسن معنوي كبير في مجموع المؤشر التقييمي الرئوي (PIS) للمرضى الذين تم علاجهم بدواء تبخير السالبيوتامول وكذلك للمرضى الذين تم علاجهم بالدواء المزيج (الابراتروبيام والسالبيوتامول) بعد 30 و 60 و90 دقيقة من وقت الدخول الى الطوارئ مقارنة بالنتائج الأولية (لحظة الدخول). عند الدقيقة ٣٠ من فترة دخول المريض لوحدة الطوارئ كان هنالك تحسن بشكل كبير بمجموع المؤشر التقييمي الرئوي

(PIS=5.60±2.77) للمرضى الذين تم علاجهم بالدواء المزيج (تبخيرالابراتروبيام والسالبيوتامول) أكثر من أولئك المرضى الذين تم علاجهم بدواء تبخير السالبيوتامول لوحده (PIS=7.32±2.18) . وكذلك وجد ان مدة العلاج والبقاء في وحدة الطوارئ اقل بشكل كبير (57.60±21.71 دقيقة) بالنسبة للمرضى المعالجين بالدواء المزيج (الابراتروبيام والسالبيوتامول) بالمقارنة مع المرضى المعالجين بدواء تبخير السالبيوتامول لوحده (77.40±16.13 دقيقة) .

الاستنتاج :

ان علاج الأطفال المصابين بنوبة الربو الحادة ذو الشده الخفيفة الى المتوسطة بدواء تبخير السالبيوتامول يحسن الحالة السريرية للمريض ويخفض مجموع المؤشر التقييمي الرئوي. وان إضافة دواء تبخير الابراتروبيام الى دواء تبخير السالبيوتامول يحسن بشكل كبير الحالة السريرية ومجموع المؤشر التقييمي الرئوي وفترة بقاء المريض في وحدة الطوارئ أكثر من العلاج بدواء السالبيوتامول لوحدة.

Introduction:

Asthma is the most common chronic childhood illness in developed countries [(1)]. Recurring asthma-like symptoms were stated in about 32% of preschool children in the United States and Europe [(2)]. Epidemiologic data approximation that nearly seven million children in the United States are diagnosed with asthma [(3)]. In Iraq, the International Study of Asthma and Allergies in Childhood recorded the prevalence of childhood asthma as 16.3% in primary school children [(1)].

Asthma is characterized by recurring attack of wheezing, shortness of breath, chest tightness, and coughing; sputum may be produced from the lung by coughing but is often hard to bring up [(4)]. Throughout recovery from an attack, it may look pus-like due to high levels of eosinophils [(5)]. Asthma severity can be assessed clinically or by pulmonary function test [(6)]. Several clinical asthma severity scores have been designed for use in the acute care setting to evaluate initial exacerbation severity [(7)]. The Pulmonary Index Score (PIS) is an asthma score based on five clinical variables: respiratory rate, inspiratory to expiratory ratio, degree of wheezing, accessory muscle use, and oxygen saturation (table 1) [(7)]. Each variable is assigned

a score from 0 to 3. Total scores range from 0 to 15. As an over-all rule, a score under 7 indicate an exacerbation of mild severity, a score of 7 to 11 indicates an exacerbation of moderate severity and a score of ≥12 indicates a severe attack. The PIS has been validated and used as an outcome measure in several clinical trials [8-9]. It can be used to assess initial severity, judge response to treatment, and facilitate admission and discharge planning [10]

Table 1: The Pulmonary Index Score [7]

Score	Respiratory rate 5 years or below	Respiratory rate 6 years or above	Wheezing	Inspiratory/ expiratory ratio	Accessory muscle use	Oxygen Saturation
0	≤30	≤20	None	2:1	None	99-100
1	31 – 45	21 - 35	End expiration	1:1	+	96-98
2	46 – 60	36-50	Entire expiration	1:2	++	93-95
3	> 60	>50	Inspiration and expiration or Silent chest	1:3	+++	<93

For patients with mild asthma exacerbation (PIS <7), treatment include salbutamol inhalation therapy administered via small volume nebulizer (SVN) at a dose of 0.15 mg/kg (minimum 2.5 mg and maximum 5 mg per dose). If recurrent doses are required, they should be given every 20 to 30 minutes for three doses [11]. For patients with moderate asthma exacerbation (PIS 7 to 11). Administration of supplemental oxygen if oxygen saturation ≤92 percent in room air [12]. Salbutamol nebulization (0.15 mg/kg, maximum 5 mg) [13, 14] alternate with ipratropium bromide nebulization (250 mcg/dose if <20 kg; 500 mcg/dose if >20 kg) each 20 to 30 minute for three doses or continuously [15, 16]. Administration of systemic glucocorticoids soon after arrival in the ER [8]. Administration of intravenous magnesium sulfate (75 mg/kg, maximum 2.5 g administered over 20 minutes) if there is lack of clinical improvement or clinical deterioration despite treatment with beta-agonists, ipratropium bromide, and systemic glucocorticoids [17]. B_2 adrenergic receptors are present in high density in airway smooth muscle

cells. B_2 agonists act by binding to the B_2AR. Interaction of the receptor with intracellular G proteins stimulates the creation of intracellular cyclic adenosine monophosphate. This leads to activation of protein kinase A, which results in phosphorylation of various targets facilitating smooth muscle relaxation [18]. Inhaled selective β_2-agonists with an intermediate duration of action are the most commonly prescribed asthma medications in the world [19] Tremor is the most frequent acute side effect and is more noticeable with oral therapy than with inhaled agents [20].

Ipratropium bromide was presented into the management of obstructive airway diseases in the mid-1970s. Numerous studies have been doing in order to assess the effectiveness of this compound in asthma, in comparison with short-acting β_2-agonsists. In almost all studies, salbutamol, both in solitary and increasing doses, determined a better bronchodilation than ipratropium bromide in asthmatic subjects; while salbutamol additional to ipratropium bromide was effective in determining a significant improvement in FEV_1 [21]. Inhaled ipratropium has a relatively slow onset and long duration of action compared with beta-2 agonists [22]. In asthmatics, inhaled ipratropium produces 50 percent of its bronchodilator effect within 3 minutes, 80 percent in 30 minutes, and reaches its peak bronchodilator effect within approximately 90 minutes [23].

Aim of the study: To evaluate the effects of salbutamol nebulizer versus salbutamol plus ipratropium bromide in the children with acute asthma exacerbation attack**.**

Patients and methods:

This is a randomized double blind standard control clinical study, conducted on hundred patients presented to the emergency department with acute attacks of asthma, in Kerbala teaching hospital of pediatrics from 1st of November 2015 to the end of November 2016. Patient selection was done according to specific inclusion and exclusion criteria

Inclusions criteria:

1- Asthmatic children during acute attack.

2- Age 12 month -12 years.

Exclusions criteria:

3- Patient with severe acute attack of asthma.

4- Patients received corticosteroids therapy in the last 24 hours.

5- Patients received salbutamol or ipratropium in the last 12 hours.

6- Patient with cardiovascular disease.

7- Patient with chronic disease like chronic renal failure, chronic lung disease, diabetes mellitus etc.

Study Protocol: Selected patients were interviewed in the emergency department using special questionnaire designed for this study. Baseline (PIS) was done (table 1) [7] for each patient then randomly allocated into one of the following groups:

Group A: *Salbutamol group (standard group):* This group included 50 patients received salbutamol dose (2.5 mg) every 30 minute during their stay in the emergency department by nebulizer with face mask.

Group B: *Ipratropium plus salbutamol group* (combination group): This group included 50 patients received ipratropium solution (250 mcg) per dose mixed with salbutamol inhaler (2.5 mg) per dose via jet nebulizer with face mask. Each patient received this dose every 30 minute during his stay in the emergency department.

Randomization was performed according to the patient's emergency card number; odd numbers got into group A, even numbers into group B. Assessment of asthma severity was done for each patient according to pulmonary index score (table 1) [7].

Drug preparation: The dose was prepared in the pharmacy of the emergency department blindly from the researcher immediately before administration as follow:

- *Salbutamol dose:* 0.5 ml (2.5 mg) of salbutamol solution was mixed with 3 ml normal saline in a 5 ml disposable syringe and labeled with letter (A) after shaking.
- *Ipratropium plus Salbutamol dose:* 2ml (250 mcg) of ipratropium bromide was mixed with 0.5 ml (2.5 mg) of salbutamol solution that is further mixed with 1 ml normal saline in a 5 ml disposable syringe and labeled with letter (B) after shaking.

Ipratropium bromide solution 250 mcg/2 ml (Atrovent®) was obtained from Boehringer Ingelheim, Germany and Ventolin® respiratory solution 20 ml (contain salbutamol 5mg/ml) was obtained from GlaxoSmithKline, UK.

Patients follow up: Pulmonary index score (PIS) was measured for each patient every 30 minute (at baseline, 30, 60, 90 minute), and their fate were determined whether discharged or continue treatment according to (PIS).

Signs of improvement each patient included:

1- Respiratory rate less or equal to 30 /min for age above 5 years [11].

2- Respiratory rate less or equal to 40 /min for age below or equal to 5 years [11].

3- No sign of dyspnea.

4- O_2 saturation increased more than 92% in room air.

Ethical consideration: Study protocol was approved by the Scientific Council of Pediatrics of the Arab Board for Health Specialization. Parents' agreements were obtained prior to participation. Data were kept confidentially; names of participants were replaced with identification codes and the data were not disclosed to unauthorized personnel.

Statistical analysis: Data were transformed into computerized database and analyzed using the Statistical Package for Social Science (SPSS) version 22, 2013, USA. Descriptive statistics were presented as frequencies (No.), percentage (%), mean and standard deviation. Appropriate statistical test was used accordingly; Chi square test was used to assess significance of association. Level of significance (P. value) was set at 0.05 to be considered as significant.

Results:

One hundred patients were enrolled in this study, 50 patients in salbutamol group and 50 patients in combination group (ipratropium bromide + salbutamol). The major demographic characteristic of patient was shown in table (2).

Table 2: Demographic characteristics of study groups.

Characteristics	Salbutamol Group (N=50)	Salbutamol + ipratropium Group (N=50)	P value
Age (year) Mean ± SD	5.1±2.3	6.09 ±2.27	0.043
Male Gender	25 (50%)	26 (52%)	0.84
Weight (Kg) Mean ± SD	19.7±6.7	22.4±6.2	0.04
Height (cm) Mean ± SD	104.3±14.8	114±14.7	0.003
Patients on controller therapy	12 (24%)	18 (36%)	0.19

The PIS was significantly ($p<0.05$) reduced for patients treated with salbutamol in ER after 30,60 and 90 minutes as compare with their score at baseline, 30 and 60 minute respectively as shown in table (3).

Table 3: Mean change in PIS after treatment with salbutamol during ER admission.

Patient remain in ER	Assessment time (minute)	PIS (mean ± SD)	PIS reduction (%)	P value
At 30 min (N=50)	0	9.40±1.70	22.1	0.001
	30	7.32±2.1*		
At 60 min (N=48)	30	7.43±2.14	26.6	0.001
	60	5.45±2.0#		
At 90 min (N=28)	60	5.60±1.77	41.4	0.001
	90	3.28±2.86¥		

* Significant difference as compared with PIS at time 0
# Significant difference as compared with PIS at time 30
¥ Significant difference as compared with PIS at time 60

The PIS was significantly ($p<0.05$) reduced for patients treated with ipratropium bromide + salbutamol in ER after 30, 60 and 90 minute as compare with their score at baseline, 30 and 60 minute respectively as shown in table (4).

Table 4: Mean change in PIS after treatment with ipratropium bromide+ salbutamol during ER admission.

Patient remain in ER	Assessment time (minute)	PIS (mean± SD)	PIS reduction (%)	P value
At 30 min	0	9.20±1.98	39.1	0.001

(N=50)	30	5.60±2.77*		
At 60 min (N=35)	30	6.74±2.51	40.6	0.001
	60	4.00±2.61#		
At 90 min (N=11)	60	7.27±2.19	53.7	0.001
	90	3.36±2.72¥		

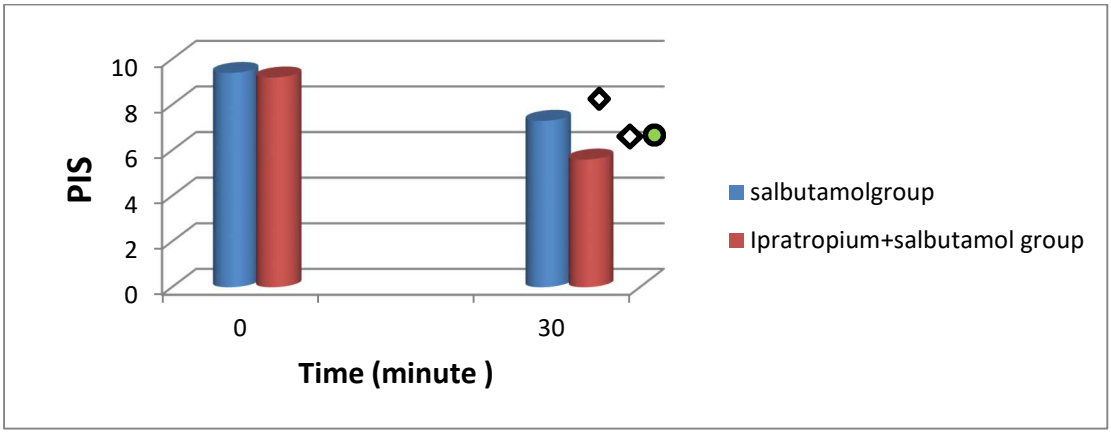
* Significant difference as compared with PIS at time 0
# Significant difference as compared with PIS at time 30
¥ Significant difference as compared with PIS at time 60

At baseline, there was no significant difference (P>0.05) in PIS between patients in salbutamol group and in patients with combined group (ipratropium bromide+ salbutamol) group. After 30 minutes, patients who were treated with combination of ipratropium bromide + salbutamol had significantly lower PISs than those treated with salbutamol alone as shown in table (5) and figure (1).

Table 5: Effects of treatment with salbutamol and ipratropium + salbutamol on pulmonary index score after 30 minute from ER admission.

Time	Group (N=50)	PIS (mean± SD)	PIS reduction (%) from base line	p. value
0 min (baseline)	Salbutamol	9.40±1.70		0.590◦
	ipratropium + salbutamol	9.20±1.98◦		
30 min	Salbutamol	7.32±2.18*	22.1	0.001#
	ipratropium + salbutamol	5.60±2.77*#	39.1	

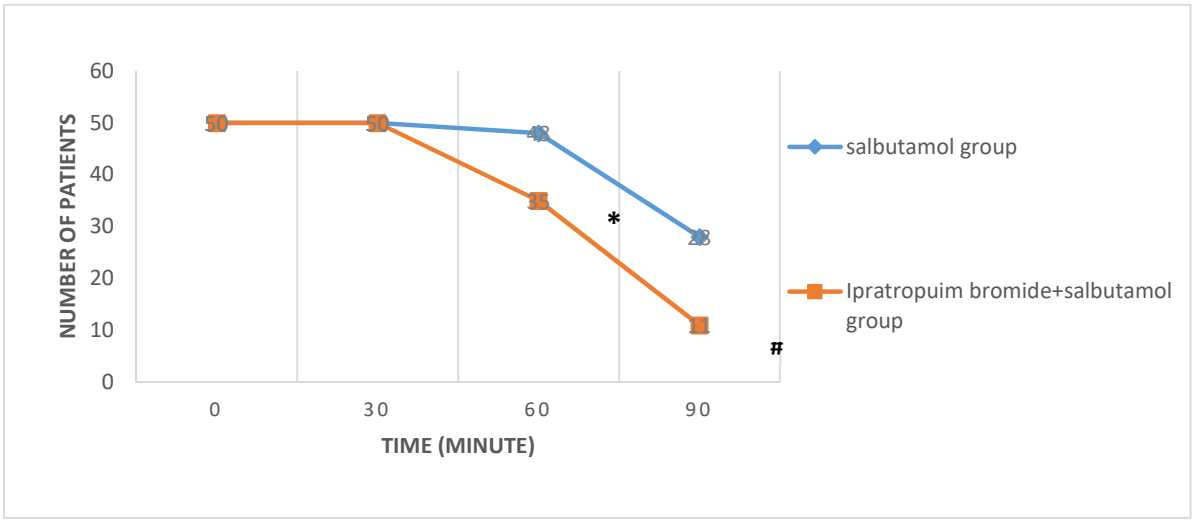
* Significant difference as compared with PIS at baseline.
# Significant difference as compared with PIS of salbutamol group at time 30 min.
◦ No significant difference as compared with PIS of salbutamol group at baseline.



◇ Significant difference (p <0.05) as compare with baseline
Significant difference (p <0.05) as compare with salbutamol group at 30 minute

Figure 1: Effects of treatment with salbutamol and ipratropium + salbutamol on pulmonary index score after 30 minute from ER admission.

At 30-minute from admission to ER the number of patients who stay in emergency room were 50 for each group with no significant difference in numbers between these two groups (*P*>0.05). After 60 minute (from ER admission), the number of patients in salbutamol group decreased to 48 patients and to 35 for ipratropium bromide + salbutamol group with significant difference in number of patients (p <0.05). At end of 90 minute there were 28 patients from salbutamol group and only 11 patients from combination group with significant difference in number of patient between groups (p <0.05) as shown in figure 2:



* Significant difference (p <0.05) as compared with no. of pt. in salbutamol group at 60 min

Significant difference (p <0.05) as compared with no. of pt. in salbutamol group at 90 min

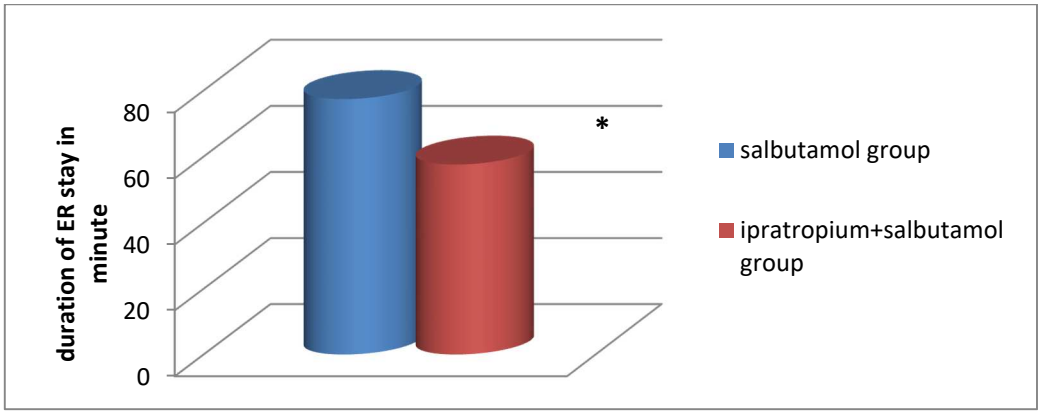
Figure 2: Number of patients stay in emergency unit during treatment with salbutamol and ipratropium bromide + salbutamol.

The mean duration of stay in ER was significantly shorter (p <0.05) in patient treated with nebulized ipratropium bromide + salbutamol as shown in table (6) and figure (3).

Table 6: Effects of treatment on duration of ER stay.

Group	N	Duration of ER stay in minute (Mean ± SD)	p value
salbutamol	50	77.40±16.13	0.0001
ipratropium + salbutamol	50	57.60±21.71*	

* Significant difference as compared with duration in salbutamol group



* Significant difference (p <0.05) as compared with duration in salbutamol group

Figure 3: Effects of treatment on duration of stay in ER.

Discussion:

In this study, we found that the fixed doses of nebulized salbutamol improved pulmonary index score significantly through three session intervals during ER admission and decreased number of patient who stay in hospital (table 3) which consistence with many guidelines as 1st line management in acute asthma exacerbation [24, 25].

The fixed dose of combined ipratropium bromide+ salbutamol improved the pulmonary index score at 30, 60 and 90 minute interval with significant clinical improvement ($p<0.05$) and reduction in PIS reached to 53.7 % at 90 min as show in table 4. On comparing the two groups at specific time intervals, we found that ipratropium bromide with salbutamol showed significant improvement in pulmonary index score during the first 30 minute of treatment ($p<0.05$) with about 17 % less than salbutamol group, these results are in line with a meta-analysis [53], and two randomized controlled trials; These studies suggest that the addition of multiple doses of anticholinergic agents to β_2-agonist therapy in the initial treatment of children with severe asthma exacerbations had gave a greater improvement in clinical state and lung function with less frequent hospital admission [27, 28]. A large recent systemic review by Pollock, Michelle et al 2016 [29] demonstrate the efficacy of short-acting beta-agonist (salbutamol) delivered by metered-dose inhaler as first-line therapy for younger and older children (hospital admission decreased by 44% in younger children, and ER length of stay decreased by 33 minutes in older children). Short-acting anticholinergic (ipratropium bromide) should be added to salbutamol for older children in severe cases (hospital admission decreased by 27% and 74% when compared to salbutamol and ipratropium bromide alone, respectively) and marked improvement in asthma clinical score. While a recent study in Pakistan by Memon BN show that after treatment for maximally three doses of drugs 15 minutes apart, 93% of children treated with ipratropium bromide plus salbutamol showed improvement in clinical scores while in salbutamol only 84% of children showed improvement in clinical score, even with this improvement, the combination of nebulized ipratropium bromide and salbutamol

failed to give significant reduction than salbutamol group in acute exacerbation attack [30]. This is may be type of analytic study that depended on the percentage of patients improved not on the mean change in PIS so it lake the actual deference between two study groups. In the present study, the ER beds usage had decreased significantly ($p<0.05$) after 60 minute from addition of ipratropium bromide to the conventional therapy (salbutamol) in our hospital (figure 2), another important outcome was ipratropium group had shorter treatment time (mean, 57.6 minutes, vs salbutamol, 77.4 minutes) as shown in table 6; and this result agreed with Zorc, J J [31], who showed that the addition of three doses of ipratropium to an emergency department treatment protocol for acute asthma was associated with reductions in duration and amount of treatment before discharge. On the economic side, asthma treatment constitutes a major burden on health care resources [32] and causes parenteral absence from work and children school absence. So, shortening the hospital length of stay provides significant social and economic benefits in saving health service resource [33].

Conclusions:

Treatment of asthmatic children with mild to moderate acute exacerbation attacks with combination therapy of ipratropium plus salbutamol nebulizer improved the clinical condition, lowered pulmonary index score, and significantly shorten the duration of stay in emergency room more than those patients who treated with salbutamol nebulizer alone.

Recommendations:

Based on the findings of the present study, we recommend using ipratropium bromide in combination with salbutamol in the management of mild to moderate acute attack of asthma. Further studies with larger sample size, using lung function test for patient assessment is also recommended.

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