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Original Article

Efficacy of salbutamol-ipratropium bromide nebulization compared to salbutamol alone in children with mild to moderate asthma attacks

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Abstract

Background The efficacy of salbutamol-ipratropium bromide nebulization in children with moderate asthma attacks remains unclear, and studies on patients with mild attacks have been relatively few, especially in Indonesia. However, it is common practice for this drug combination to be given to patients with mild-moderate asthma attacks.

Objective To compare the efficacy of salbutamol-ipratropium bromide nebulization to salbutamol alone in children with mild to moderate asthma attacks.

Methods This single-blind, randomized clinical trial was held in the Department of Child Health at Cipto Mangunkusumo Hospital, the Tebet Community Health Center, and the MH Thamrin Salemba Hospital on children aged 5-18 years with mild to moderate asthma attack. We randomized subjects to receive either 2.5 mg salbutamol plus 0.5 mg ipratropium bromide (experimental group) or 2.5 mg salbutamol alone (control group). Nebulization was given twice, with a 20 minute interval between treatments. We assessed clinical scores, vital signs, oxygen saturations, and peak flow rates (PFRs) at baseline, and every 20 minutes up to 120 minutes post-nebulization.

Results A total of 46 patients were randomized to either the experimental or the control group. Subjects had similar baseline measurements. At 20 minutes post-nebulization, the percentage increase of PFR was 19% higher in the experimental group (P=0.01, 95% CI 1.8 to 47.2). The proportion of PFR reversibility was 27% higher in the experimental group, although this result was statistically insignificant (P=0.06, 95% CI 0.03 to 0.52). There were no significant differences in clinical scores, oxygen saturations, respiratory rates, or hospitalization rates between the two groups. Side effects also did not differ significantly.

Conclusion Salbutamol-ipratropium bromide nebulization improved PFR measurements better than salbutamol alone. However, other clinical parameters were not significantly different between the two groups. **[Paediatr Indones. 2012;52:200-8]**.

Keywords: *children, mild to moderate asthma attack, ipratropium bromide, salbutamol*

Asthma is global health problem in children, and is increasing in prevalence, even though the pathogenesis, pathophysiology, and management of asthma is well understood. The National Health Interview Survey in the United States reported an asthma prevalence of 7.5% in 1995.[1] In Indonesia, Rahajoe *et al*. reported asthma prevalence to be 6.7%.[2]

Controversies in asthma management may increase morbidity and mortality of patients. The addition of ipratropium bromide for patients with asthma attacks has been controversial. Beta$_2$-

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agonists are potent bronchodilators, but multiple or large doses may cause adrenergic side effects.[3-6] However, ipratropium bromide is an anticholinergic bronchodilator with a slower onset, longer duration of action, and less adrenergic side effects compared to those of beta$_2$-agonists.[3,6,7] Previous studies have shown that a combination of salbutamol and ipratropium in patients with severe asthma attacks improve lung function and clinical score, while lowering emergency department (ED) admission duration and hospital admission rates.[8,9] Other studies have also reported salbutamol-ipratropium bromide superiority in patients with moderate attacks,[10,11] while studies on its use in patients with mild asthma attacks have been few.[10,12,13] Salbutamol-ipratropium nebulization has commonly been given to patients with mild to moderate asthma attacks, although only one Indonesian study to date has been published on this subject.[14]

We aimed to compare the efficacy of salbutamol-ipratropium nebulization with salbutamol alone in pediatric patients with mild to moderate asthma attacks. We measured and compared clinical scores, peak flow rates, oxygen saturations, respiratory rates, and hospital admission rates of the two groups.

Methods

This study was designed as a single-blind, randomized, clinical trial performed from September 2010-March 2011 at the Community Health Center of Tebet District, and the EDs of Cipto Mangunkusomo Hospital and MH Thamrin Salemba Hospital. We compared the effects of nebulization with salbutamol-ipratropium combination to those of salbutamol alone.

Patients aged 5-18 years who visited the ED with mild to moderate asthma attacks, classified according to Schuh's asthma clinical score,[9] were eligible for enrollment. We excluded patients with signs of respiratory failure, need of intensive care management, heart abnormality, pneumonia or other respiratory disorders altering lung function, ocular disorder altering intraocular pressure or pupillar response (as diagnosed by history-taking and physical examination), hypersensitivity to ipratropium or salbutamol, and those who had received ipratropium bromide treatment within the 36 hours prior to enrollment. Subjects' parents provided informed consent.

We consecutively assigned subjects to receive either salbutamol-ipratropium bromide (experimental group) or salbutamol alone (control group), according to a drug sequence table generated by block randomizations of six. This table was kept by the principal investigator (PI) to keep the subjects blinded to their allocated group.

Subjects were given either 2.5 mg salbutamol with 0.5 mg ipratropium bromide (Combivent®) or 2.5 mg salbutamol (Ventolin®) nebulization in 3-5 ml saline. Subjects were given two doses by ultrasonic nebulizer (Omron NE-C29) via face mask, with a 20 minute interval between treatments. The duration of each nebulizer treatment was about 10 minutes. At enrollment, subjects' baseline data was collected including demographic characteristics (age, sex, and nutritional status), asthma history, treatment history, asthma comorbidities (allergic rhinitis or sinusitis), duration of current symptoms, and asthma severity. We also measured baseline clinical parameters, including Schuh's clinical scores, vital signs, PFRs by mini peak flow meter (Breath-Taker, Australia, reproducibility 8.4%, SD 27 L/m), and oxygen saturation by pulse oxymetry (Oxy3, OneMed). Clinical response was assessed every 20 minutes, until 2 hours post-nebulization, including the same parameters measured at baseline. For patients with moderate attacks, we planned to also measure blood gas analysis (BGA) twice, at baseline and at 2 hours after treatment, though most patients declined. PFR was measured by forced expiration maneuver (patient twice performed forced expiration after maximal inspiration with at least a 5-second interval between forced expiration). Only the best value was recorded. Patients with inadequate clinical response after 2 hours post-treatment were admitted to the hospital.

If the principal investigator (PI) was absent when an asthma attack patient came to ED, the clinical score at baseline was measured by a research assistant or by trained ED attending physicians. When a subject enrolled, the PI was called by phone for study group random allocation instructions. By the time the second nebulization was finished, the PI would have arrived at the ED to continue data measurements. Prior to the study, interrater reliability for baseline

clinical scoring was assessed by comparing the PI's ratings to those of a research assistant on 6 patients. Individual severity scores were summed and divided into three severity groups as follows: mild (total score 1–3), moderate (total score 4–6) or severe (total score 7–9) (**Table 1**). Interrater reliability was measured using these severity subgroups, with Kappa=0.6.

The primary outcome was nebulization efficacy, measured by several parameters including decreased clinical score, increased PFR, increased oxygen saturation, decreased respiratory rate, and decreased percentage of hospital admission. PFR was measured as the percentage increase from baseline. PFR reversibility was defined as a PFR increase >12% from baseline. The proportion of patients with PFR reversibility in each group was also recorded. Secondary outcomes were blood gas values before and after treatment, and side effects of medications.

The required sample size was determined by a formula of mean difference of two independent groups, with α=5% and power of 80%. Since a previous study showed that the standard deviation of mean change in clinical asthma score between the salbutamol-ipratropium and salbutamol groups was 1.5,[9] the clinically significant difference was set at 1.5. Therefore, 16 patients per study group, or a total of 32 patients, were needed for this study.

Differences in clinical scores, PFRs, oxygen saturation, and respiratory rates between groups were analyzed by independent t-test, or Mann-Whitney test if the data had an abnormal distribution. Differences in PFR reversibility, hospital admission, and side effects were analyzed by Chi-square test or Fisher's exact test. We performed intention-to-treat analyses and considered P<0.05 to be statistically significant.

This study was approved by The Medical Research Ethics Committee, Faculty of Medicine, University of Indonesia.

Results

A total of 46 patients were enrolled after 6 patients were excluded due to severe asthma attack (3 patients), had received ipratropium bromide within the prior 36 hours (2 patients) or had a heart abnormality (1 patient). Of the 46 subjects, 32 had mild asthma attacks (16 patients were allocated to each group), while 14 patients had moderate asthma attacks (7 were allocated to each group). All baseline parameters were similar between the two groups (**Table 2**).

At 40, 60, and 120 minutes after nebulization, clinical scores decreased more in the experimental group, but they were not statistically or clinically different from the control group by Mann-Whitney test (**Table 3**). In subjects with moderate attacks (n=14), we found an apparent difference in the mean decrease of clinical scores between the two groups. The 1.58 point difference between the two groups seemed substantial, but statistical significance could not be established because of inadequate sample size (**Table 3**).

PFR data was analyzed for 40 patients, since 6 patients failed to complete PFR measurements due to their clinical conditions. At 20-120 minutes, we found higher PFR percentage increases from baseline in the experimental group than in the control group. The median difference at 20 minutes was 19% (95%CI 1.80 to 47.18; P=0.012) and the median differences at 40, 60, and 120 minutes were all 25% (data was abnormally distributed) (**Table 4**). Statistical significance was observed only at the 20-minute time point (P=0.012). In mild attack subjects alone (n=30), we found mean difference of 15,8% at 20 minutes (95% CI 1,05 to 30,31; P=0,05; **Table 4**). In moderate subjects alone (n=10), we found more than 50% mean difference at the beginning and final observation, but statistical analysis could not be performed **(Table 4)**.

Table 1. Schuh's clinical asthma score [9]

Score	Accessory muscle score	Wheeze score	Dyspnea score
0	No retractions	No wheeze and moving air well	Dyspnea absent
1	Intercostal retractions	End-expiratory wheezes	Normal activity and speech; minimal dyspnea
2	Intercostal and suprasternal retractions	Panexpiratory + inspiratory wheezes	Decreased activity; 5-8 word sentences; moderate dyspnea
3	Nasal flaring	Wheezes audible without stethoscope	Concentrate on breathing; <5 word sentences; severe dyspnea

Mild attack: total score 1-3; moderate attack: total score 4-6; severe attack: total score 7-9

Table 2. Subjects' baseline demographics, asthma history and clinical parameters

Parameters	Control (n= 23)	Experimental (n=23)
Mean age, years (SD)	11.39 (2.56)	11.07 (3.29)
Male gender, n	12	11
Obese, n	1	2
Onset of asthma > 5 years ago, n	13	13
Asthma severity: infrequent attack episodes, n	14	15
Asthma attack severity: mild attack, n	16	16
Median duration of current symptoms, days (range)	2 (1-7)	1 (1-7)
Previous prophylaxis, n	2	3
Current non-steroid, non- ipratropium inhalant use, n	10	7
Current steroid use, n	2	2
Asthma comorbidities (allergic rhinitis and/or sinusitis), n	8	5
Median initial clinical score, (range)	2 (1-4)	3 (1-6)
Median initial peak flow rate, liters/min (range)	175 (50-350)	100 (50-300)
Median initial oxygen saturation, % (range)	97 (96-99)	98 (96-99)
Mean initial respiratory rate, x/min (SD)	28.76 (6.24)	29.42 (7.11)
Mean initial heart rate, x/min (SD)	102.19 (12.54)	103.74 (20.03)

Table 3. Comparative median/mean decreases in clinical score

Subjects	Time at evaluation	Decrease in clinical score		P	95% CI
		Control (n= 23) median (range)	Experimental (n=23) median (range)		
Mild to moderate attack	20 minutes	2 (1-4)	2 (1-4)	0.560	-0.40 to 0.57
	40 minutes	2 (1-5)	3 (1-6)	0.775	-0.55 to 0.81
	60 minutes	2 (1-5)	3 (1-6)	0.524	-0.42 to 1.12
	120 minutes	2 (1-5)	3 (1-6)	0.414	-0.34 to 1.29
		Control (n= 7) mean (SD)	Experimental (n= 7) mean (SD)		
Moderate attacks only	20 minutes	2.14 (0.90)	2.43 (0.98)	Statistical analysis was not performed due to inadequate number of subjects	
	40 minutes	3.57 (0.98)	4.14 (1.07)		
	60 minutes	3.71 (0.95)	4.86 (1.07)		
	120 minutes	3.71 (0.95)	5.29 (0.76)		

95% CI measured by a formula using mean value

We observed a higher proportion of subjects with PFR reversibility in the experimental group (17/19 subjects) than in the control group (13/21 subjects) at 20 minutes. The difference between groups was 0.27 (95% CI 0.026 to 0.524; P=0.069). At 40 to 120 minutes, there were similarly no significant differences in proportions of subjects with PFR reversibility (**Table 5**). In subjects with mild attacks alone (n= 30), there was also no difference between groups (**Table 5**), while in subjects with moderate attacks alone (n= 10), reversibility tended to be higher in the experimental group, but the sample size was too small to analyze (**Table 5**).

Before intervention, all subjects had oxygen saturation >95%, therefore, oxygen therapy was not needed. There were no differences in oxygen saturation between the two groups. We also found no significant difference in the decrease of respiratory rates between the two groups (**Table 6**) In moderate asthma attack subjects alone (n= 14), there was a greater decrease in respiratory rates in the experimental group. These differences were 4 x/minutes at 20 and 40 minutes, and 6x/minutes at 60 and 120 minutes, which were clinically quite apparent (**Table 6**) but statistical analyses were not performed due to lack of subjects.

Two patients with moderate asthma attack from the control group responded inadequately at 120 minutes, requiring hospital admission. These 2 subjects were given ipratropium bromide nebulization and intravenous steroids. They were analyzed in

the control group, since we used intention-to-treat analyses. The number of hospital admissions was higher in the control group (2/23 subjects) than in the experimental group (0/23 subjects), but this difference was not statistically significant (P=0.489) (**Table 7**).

Table 4. Comparative median PFR percentage increase

Subjects	Time at evaluation	Control (n=21) % increase, (range)	Experimental (n=19) % increase, (range)	P*	95% CI
Mild to moderate attack	20 minutes	14.28 (0-100)	33.33 (8.33-200)	0.012	1.80 to 47.18
	40 minutes	25 (7.14-100)	50 (8.33-200)	0.114	1.61 to 54.17
	60 minutes	25 (11.1-100)	50 (8.33-300)	0.115	4.46 to 83.59
	120 minutes	25 (11.1-100)	50 (8.33-200)	0.115	4.46 to 83.61
		Control (n=16) % increase, (range)	Experimental (n=14) % increase, (range)	P*	95% CI
Mild attacks only	20 minutes	13,39 (0-57,14)	29,16 (8,33-100)	0.058	1.05 to 30.31
	40 minutes	22,5 (7,14-60)	50 (8,33-100)	0.234	-2.5 to 40.96
	60 minutes	25 (11,11-100)	50 (8,33-200)	0.531	-10.56 to 49.46
	120 minutes	25 (11,11-100)	50 (8,33-200)	0.531	-10.56 to 49.46
		Control (n=5) % increase, (range)	Experimental (n=5) % increase, (range)		
Moderate attacks only	20 minutes	16,7 (0-100)	66,7 (20-200)	Statistical analyses was not performed due to lack of subjects	
	40 minutes	50 (16,7-100)	100 (20-200)		
	60 minutes	50 (16,7-100)	166,7 (60-300)		
	120 minutes	50 (16,7-100)	166,7 (60-300)		

*Mann-Whitney test. CI was measured by formula using mean value

Table 5. Comparative proportions of PFR reversibility (defined as PFR increase ≥12% from baseline)

	Reversibility at	Control (n=21)	Experimental (n= 19)	P*	95% CI
Mild to moderate attacks	20 minutes	13	17	0.069[q]	0.026 to 0.524
	40 minutes	19	17	1[q]	-0.409 to 0.431
	60 minutes	20	17	0.596[q]	-0.107 to 0.223
	120 minutes	20	17	0.596[q]	-0.107 to 0.223
		Control (n=16)	Experimental (n= 14)	P	
Mild attacks only	20 minutes	10	12	0,226[a]	Not measured
	40 minutes	14	12	1[b]	
	60 minutes	15	12	0,586[b]	
	120 minutes	15	12	0,586[b]	
		Control (n=5)	Experimental (n= 5)		
Moderate attacks only	20 minutes	3	5	Statistical analysis was not performed due to lack of subjects	
	40 minutes	5	5		
	60 minutes	5	5		
	120 minutes	5	5		

a Chi-square test b Fisher's exact test

Table 6. Comparative median respiratory rate decrease

	Time at evaluation	Control (n=23)	Experimental (n= 23)	P*	95% CI
Mild to moderate attacks	20 minutes	4 (2-18)	4 (0-8)	0,907	-2,86;1,12
	40 minutes	6 (4-20)	8 (1-16)	0,585	-2,19;2,79
	60 minutes	6 (4-20)	8(1-16)	0,602	-2,40;3,19
	120 minutes	6 (4-20)	8(1-16)	0,602	-2,41;3,18
		Control (n=7)	Experimental (n= 7)		
Moderate attacks only	20 minutes	4 (4-16)	8 (4-8)	Statistical analysis was not performed due to lack of subjects	
	40 minutes	6 (4-16)	10 (8-12)		
	60 minutes	6 (4-18)	12 (8-12)		
	120 minutes	6 (4-18)	12 (8-12)		

* Mann-Whitney test; CI measured by formula using mean value

Table 7. Comparative proportion of hospitalization

	Control (n= 23)	Experimental (n= 23)
Hospitalization	2	0
No hospitalization	21	23

P=0.488 (Fisher's exact test)

Of 14 patients with moderate attacks, only 2 consented to BGA examination. The first patient agreed to arterial puncture after the intervention, and the second patient agreed before the intervention. In both subjects, we found decreased pressure of oxygen in arterial blood (PaO_2) (33.6 and 31 mmHg, respectively) and low HCO_3 (21 and 19 mmol/L, respectively) , while pH, PaO_2 and oxygen saturation were still normal.

We found the side effect of mouth mucosal dryness to be of similar proportions in both groups. The unilateral decrease of light pupillar response was found in 2 patients from the experimental group at 20 minutes, but spontaneously resolved at 40 minutes. The proportion of subjects with tachycardia was highest at 20 minutes, but did not differ between groups. Tachycardia resolved with time.

Discussion

This study had some limitations. In this single-blinded study, investigators were not blinded, but subjects were. Ideally, the study should be double-blinded, since we used a subjective parameter of efficacy (clinical score). However, the other efficacy parameters (PFR, oxygen saturation, respiratory rate, and proportion of hospital admission) were objectively measured. Also, the PFR could not be measured in 6 patients, but the remaining sample size was still adequate for most statistical analyses. In addition, we planned to measure BGA in all subjects with moderate attacks, but most subjects refused the arterial puncture. Since Carruthers *et al.*[15] showed that respiratory failure was unlikely in patients with oxygen saturation >92%, BGA was not necessary unless otherwise clinically indicated.

In our study, interrater reliability could only be measured between the PI and a research assistant on 6 patients, due to limitations of time and sample size. Our Kappa was 0.6 (0.6-0.8 was considered sufficient). The same clinical score was used by previous studies[9,10] with Kappa values ranging from 0.6 to 0.9, similar to that of our study.

The required minimal sample size was 32 subjects, but at the end of the study, we had more subjects to be analyzed. We attempted to subgroup analyses for different attack severities. However, a subanalysis could only be performed on subjects with mild attacks due to insufficient number of subjects with moderate attacks. Therefore, we analyzed data of mild and moderate attack subjects as a whole, while trying to demonstrate clinical differences in each subgroup. The low number of asthma attack patients at our public facilities may be due to increasing numbers of private health centers with nebulization facilities as well as better maintenance treatment for asthma patients.

Demographic and clinical parameters that may influence the clinical response to nebulization treatment were assessed at baseline, and found to be similar in the two groups. We observed an insignificant difference in clinical scored throughout the study between the two groups (median difference of 1 point). Similarly, Rayner *et al.*[16] reported that ipratropium bromide given after beta$_2$-agonist resulted in a reduced synergistic effect. Furthermore, Kumaratne *et al.*[17] reported that in young subjects (4 months-6 years) assumed to have a predominant bronchospasm on peripheral small bronchi, ipratropium bromide was less effective.

In our analysis of subjects with moderate attacks alone, we found a greater decrease in clinical score in the experimental group than in the control group (mean difference 1.58 points), though further statistical analyses could not be performed due to insufficient subjects. Previous studies by Schuh *et al.*,[9] Sharma *et al.*,[18] Kartininingsih *et al.*,[14] and Qureshi *et al.*[8] also demonstrated a larger decrease in clinical score in their experimental groups. Those studies included children of younger age and greater numbers of subjects with moderately severe attacks. Our study included mostly subjects with mild asthma attacks, in which less cholinergic activity occurs. On the other hand, in subjects with moderate attacks, we found a larger difference in the decrease in clinical scores. This difference might have been more profound if the number of subjects with moderate attacks was larger.

The Global Initiative for Asthma (GINA) recommends lung function tests to confirm diagnoses and to evaluate asthma severity, as well as asthma attack severity.[19] Lung function tests generally comprise spirometry and peak flow meter examinations. We chose to use peak flow meters due to their greater availability. The reference data for predicting PFR values for age, sex, and body mass index in patients aged 5-18 years in Indonesia was insufficient, so we gauged PFR response to be the percentage of increase from baseline, and the proportion of patients with PFR increase of $\geq$12% from baseline (PFR reversibility).

We found a 19% difference (95%CI 1.80 to 47.18; P=0.012) in PFR between the groups at 20 minutes. Beyond 20 minutes, we also found differences of 25%, but they were not significant. However, the increasing confidence interval suggested relevant differences beyond 20 minutes. This result was consistent with previous studies[9,20] which showed more profound differences of lung function parameters at the end of the observations, due to the slower onset of ipratropium bromide compared to that of salbutamol. Similarly, in a meta-analysis on subjects with moderate to severe attacks, Rodrigo *et al.*[11] found a difference of 12.4% in forced expiratory volume at 1 minute (FEV_1) measured by spirometry. Sharma *et al.*[18] also found a higher PFR increase percentage in the experimental group at 30 minutes to 4 hours after nebulization, in a study on subjects with moderate attacks.

In subjects with moderate attacks alone, we found a larger difference in PFR improvement (>50%) at 20 to 120 minutes, but statistical analyses could not be performed. Schuh *et al.*[9] reported that differences in FEV_1 increased as attack severity increased. Nonetheless, a significant difference in PFR increase was reported by Rayner *et al.*,[16] who gave ipratropium bromide sequentially after salbutamol, and Qureshi *et al.*[8] who completed PFR measurements in only 40% of their subjects.

We also found a greater proportion of PFR reversibility at 20 minutes in the experimental group. The difference in proportion was only 27% (95%CI 0.026 to 0.524; P=0.069), in contrast to previous studies which showed better efficacy at the end of the observation periods.[9,20] Our study included mostly patients with mild attacks and less bronchoconstriction, thus the synergistic effect of ipratropium-salbutamol was observed at just 20 minutes. At the subsequent time points, the proportion of reversibility did not further increase because maximal bronchodilatation had already occurred at 20 minutes.

Kartininingsih et al. and Qureshi et al.[8] found significant differences in oxygen saturation between their groups, in subjects with moderate to severe attacks. In contrast, most of our subjects had mild attacks with high oxygen saturation (96-99%) at baseline, thus clinical improvement could not be shown. Ducharme et al.[13] also reported no significant difference in oxygen saturation in subjects with mild to moderate attacks.

We observed no significant difference in decreased respiratory rates between the two groups. However, in moderate attack subjects alone, we only found a tendency of difference between the groups. Studies by Sharma *et al.*[18] and Qureshi *et al.*[20] reported a greater

decrease in respiratory rate in the experimental groups, in subjects with moderate attacks and subjects with severe attacks, respectively. Our contrasting results may be due to the smaller number of subjects with moderate attacks in our study.

Many previous studies on subjects with moderate to severe attacks reported lower hospital admission rates in the ipratropium bromide group. The difference in admission rates between groups was greatest in the most severe cases. We found a small difference in hospital admissions (2/23 in the control group vs 0/23 in the experimental group), but it was not statistically significant (P=0.489). Most of our subjects had mild attacks, and as such were less likely to be hospitalized. Furthermore, our sample size was too small to detect any differences in hospitalization rates.

An asthma attack patient may initially hyperventilate to increase oxygen uptake, thus decreasing carbon dioxide levels. If the obstruction continues, the ventilation-perfusion mismatch can no longer be overcome by hyperventilation, thus resulting in hypoxemia and hypercapnia.[5,21,22] Carruthers *et al*.[15] reported that the respiratory failure rate was only 4.2% among patients with oxygen saturation >92%. In contrast, in patients with oxygen saturation <92%, 29.4% had respiratory failure. In our study, both subjects that we performed BGA on had hypocapnia and normal oxygen saturation, consistent with previous studies.[5,21,22] The relatively low value of HCO_3 revealed a tendency towards metabolic acidosis which can be caused by the increase of plasma lactate due to increased respiratory muscle activity under hypoxic conditions. Beta2-agonist receptor stimulation may also generate gluconeogenesis, glycolyis and lipolysis, producing lactate.[23] The two subjects who had BGA assessed in this study did not show clinical signs of metabolic acidosis, despite the low value of HCO_3, thus they did not need any additional specific management.

There were 2 patients with pupil abnormalities in the experimental group. These side effects were reversible. Mouth mucosal dryness did not differ between the groups. Tachycardia was also similar between the groups, and resolved with time. Tachycardia was not only due to side effects of medications, but was also a physiologic response to mismatched ventilation-perfusion, resolving as clinical condition improved. Qureshi et al.,[8] Ducharme et al.,[13] and Rodrigo et al.[11] also reported no significant differences in side effects with the addition of ipratropium bromide.Despite the study limitations, we conclude that salbutamol-ipratopium bromide nebulization showed better efficacy compared to salbutamol alone in patients with mild to moderate asthma attacks. The PFR percentage increase and PFR reversibility at 20 minutes was better clinically for the experimental group. However, other clinical parameters of efficacy (clinical scores, oxygen saturation, respiratory rates, and hospital admission rates) were not different between groups. In subjects with moderate attacks alone, we observed a tendency to better efficacy with the addition of ipratropium bromide, based on clinical score, PFR, and respiratory rate. Nevertheless, further studies with a larger sample size for subjects with moderate attacks are necessary.

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