

ORIGINAL ARTICLE

Frequency of Hypokalemia in Patients with Salbutamol Nebulization

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Pak Pediatr J 2026; 50(1): 40-47

ABSTRACT

Objective: To determine the frequency of hypokalemia and evaluate changes in serum potassium levels following nebulized salbutamol therapy in children presenting with mild asthma exacerbation.

Study Design: Prospective pre–post analytical study conducted in a single tertiary-care pediatric emergency department.

Place and Duration of Study: Pediatric Emergency Department, Civil Hospital Karachi from 30th March 2025 to 29th September 2025.

Material and Methods: This study included 370 children aged 1–12 years presenting with mild asthma exacerbation and requiring nebulized salbutamol. Consecutive sampling was used. Children with chronic illnesses, systemic disorders, or on potassium-altering medications were excluded. Nebulized salbutamol was administered in standardized doses (2.5 mg for <20 kg and 5 mg for ≥20 kg). Serum potassium levels were measured before and 30 minutes after nebulization. Data were analyzed using appropriate statistical tests, and logistic regression was performed to identify independent predictors of hypokalemia.

Results: The mean age was 7.1 ± 2.6 years, and 60.5% were males. Mean serum potassium significantly decreased from 4.18 ± 0.46 mmol/L at baseline to 3.76 ± 0.49 mmol/L after nebulization ($p < 0.001$), with a mean decline of 0.42 mmol/L. Hypokalemia developed in 27.8% ($n = 103$) of children. Higher frequency was observed in children <5 years ($p = 0.01$), those receiving 5 mg salbutamol ($p = 0.003$), and malnourished children ($p < 0.001$). Younger age, higher dose, and malnutrition were independent predictors.

Conclusion: Nebulized salbutamol significantly lowers serum potassium and may induce hypokalemia even in mild asthma. Younger, malnourished children and those receiving higher doses are at increased risk.

Key Words: *Salbutamol, Hypokalemia, Asthma, Children, Nebulization, Serum potassium, Pakistan*

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Received for publication: Jan. 28, 2026
Revised received: March. 16, 2026
Revision accepted: March. 30, 2026

How to cite this: Sumaiya, Jamalvi W, Shaukat M, Sadiq A, Sania H, Yasamin
Frequency of Hypokalemia in Patients with Salbutamol Nebulization

DOI:
<https://doi.org/10.66347/ppj.v50i1.679>

INTRODUCTION

Asthma is a common chronic inflammatory airway disease characterized by variable airflow

obstruction and bronchial hyper-responsiveness. Acute exacerbations are among the leading causes of pediatric emergency visits worldwide. In Pakistan, asthma affects a substantial proportion

of children and represents an important public health burden.^{1,2} Nebulized short-acting β_2 -agonists such as salbutamol are the cornerstone of acute asthma management. However, β_2 -agonists can induce electrolyte shifts, particularly hypokalemia, through stimulation of Na^+/K^+ -ATPase activity and intracellular potassium redistribution. Although this effect is well documented pharmacologically, local data evaluating the frequency and clinical relevance of salbutamol-induced hypokalemia in Pakistani children with mild asthma exacerbations remain limited.^{3,4}

Short-acting β_2 -agonists such as salbutamol are still the basis for therapy in acute asthma and wheezing episodes. These agents can be administered via Metered Dose Inhalers (MDIs) or nebulization. Salbutamol is in general considered as safe and as effective, but new evidence has ignited some worries about its possible systemic adverse effects when it is administered via the process of nebulization. Cardiac arrhythmias that are serious may occur, potentially because of the reported side effects such as hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia. These electrolyte disturbances have been observed in particular. Repeated or high-dose administration can cause them within. Study reported hypokalemia, tachycardia, arrhythmia are well-known side effects of oral/parenteral β_2 -agonists.¹

International studies have highlighted this issue. For example, a study in Chandigarh, India, found that 37% of patients developed low potassium levels after receiving three nebulized doses of salbutamol over a short period, e.g.; The mean \pm SD serum potassium concentration before and after post nebulization was 4.44 ± 0.85 mEq/L and 4.01 ± 0.97 respectively.^{1,2} Similarly, research from Lahore in 2005 showed that using salbutamol alone was more likely to cause low potassium 6.4 ± 0.3 mmol/L to 5.7 ± 0.3 mmol/L at 30 minutes of duration.³ Potassium deficiency impacts the normal functioning of various organs, with the cardiovascular system, nervous system, muscles, and kidneys being the most commonly affected.⁴

While nebulized salbutamol is commonly used in children for asthma attacks, there is limited local data about its side effect, particularly how it affects blood potassium levels. Since children are

especially vulnerable to changes in electrolytes, and because such imbalances can lead to serious health problems like irregular heartbeats, it is important to study this further. By understanding these effects better in our own population, we can make more informed choices about asthma treatment and improve patient safety.

MATERIAL AND METHODS

This research was carried out as prospective pre-post analytical study in a single center at the Pediatric Emergency Department of Civil Hospital Karachi. It was conducted over six months after the formal approval of the synopsis from College of Physician and Surgeons Pakistan (CPSP) and IRB. Sample size was determined using OpenEpi software, for a 95% confidence interval with a margin of error of 5% and expected prevalence of hypokalemia was considered as 37% in children who were administered salbutamol nebulization which yielded minimum required sample size as least of total 370. Non-probability Although this approach ensured feasibility in a busy emergency setting, it may introduce selection bias and therefore represents a limitation of the study.

Children 1-12 years of any gender with asthma exacerbation, presenting to the pediatric emergency department, with a guardian who could provide written informed consent and those able to provide age-appropriate assent were enrolled. Only children who required two or more doses of nebulized salbutamol for clinical improvement were included. This criterion ensured adequate exposure to salbutamol to assess biochemical effects; however, it may preferentially select children with more persistent bronchospasm and therefore introduce spectrum bias, which is acknowledged as a potential limitation. Children whose guardians declined to participate, or who were suffering from other chronic medical conditions which are known to affect potassium homeostasis; such as children with congenital heart disease, cystic fibrosis, pulmonary tuberculosis, congenital lung malformations (CLM), diabetes mellitus or acute kidney disease were excluded. Children treated with medications influencing potassium in the body, including potassium-sparing diuretics, beta-blockers, ACE inhibitors or angiotensin receptor blockers and children with mental handicap

(trauma or other acute systemic diseases) were also excluded to avoid confounding.

Ethical clearance was obtained and confidentially as well as patient rights were protected before starting this study. Patients were potentially considered eligible at presentation and consent was parents (or guardians), when age appropriate, written informed consent; for children. All children underwent a complete standardized clinical evaluation conducted by a trained pediatrician to assess the severity of asthma and for symptoms suggestive of hypokalemia, that is, weakness or fatigue (general weakness), muscle cramps, lethargy or cardiovascular disturbances. Mild asthma exacerbation was operationally defined as the presence of wheeze with mild respiratory distress, preserved oxygen saturation (>90%), absence of severe accessory muscle use, and the ability to maintain oral intake. A validated clinical severity score such as the Pediatric Respiratory Assessment Measure (PRAM) was not used due to emergency workflow constraints. Age, sex, nutritional status (weight for age), past medical history was recorded on a structured proforma along with clinical parameters including: oxygen saturation and respiratory status.

A 2 ml venous blood sample was collected pre-salbutamol for determination of serum potassium and full blood count. Patients' samples were immediately delivered to the laboratory using routine collection protocol, for a reduced pre-analytical phase errors. Serum potassium analysis was performed using an automated ion-selective electrode electrolyte analyzer (Roche Cobas c311, Roche Diagnostics, Germany) according to standard laboratory protocols. Internal quality control procedures were performed daily to ensure analytical accuracy, and hypokalemia was defined as serum potassium <3.5 mmol/L. After baseline measurement, nebulized salbutamol (aerosolized bronchodilator) was administered with the patient sitting upright via a calibrated nebulizer device connected to well-fitting mask. Three doses were given 15 minutes apart at the following dosage: for those weighing less than 20 kg each dose was 2.5 mg, and for those more than 20 kg, each dose was 5 mg based on standard pediatric asthma guidelines. Only those children with mild dyspnea were enrolled to avoid

use of any additional drugs, such as corticosteroids or parenteral fluids, that can affect potassium level. Thirty minutes after the completion of nebulization protocol, a second venous blood sample (2 ml) was collected to repeat serum potassium concentration and complete blood count (CBC) to determine post-treatment changes.

Data were computerized and analyzed by SPSS. Double entry, cross-checking, and validation were used to minimize transcription errors as part of the data quality assurance protocol. We used descriptive statistics to describe the demographic, clinical and laboratory features. Categorical variables were reported as the frequency and percentage, while continuous variables were summarized using means \pm standard deviations or medians and interquartile ranges (IQR) after evaluation of their distribution with normality tests. The pre-treatment and post-treatment serum potassium was compared with a paired t-test for normally distributed variables or the Wilcoxon signed rank test for not-normally distributed data. The rate of occurrence of hypokalemia following salbutamol nebulization was estimated, and subgroup analyses were performed based on age, sex, nutritional status, baseline potassium values, dose of salbutamol administered and clinical severity. Relations between hypokalemia and the reference variables, clinical characteristics, weight-for-age-standard deviation score (Z-score), oxygen saturation and characteristics of treatment were first explored using chi-square or Fisher's exact test. Multivariable logistic regression analysis was performed to identify independent predictors of hypokalemia. Variables entered into the model included age group, sex, nutritional status, baseline potassium level, baseline oxygen saturation, residence (urban/rural), and salbutamol dose. Adjusted odds ratios (AOR) with 95% confidence intervals were calculated. Model adequacy was assessed using the Hosmer–Lemeshow goodness-of-fit test, and multicollinearity was evaluated using variance inflation factors (VIF). All analyses were two-tailed, and a p-value < 0.05 was considered statistically significant.

RESULTS

A total of 370 children aged 1–12 years fulfilling inclusion criteria were enrolled. All patients presented with mild asthma exacerbation and received standardized Salbutamol nebulization.

The mean age of participants was 7.1 ± 2.6 years. There were 224 (60.5%) males and 146 (39.5%) females, yielding a male-to-female ratio of 1.5:1. More than half of the participants belonged to the <5 years age group (62.7%). The majority were urban residents (71.6%). Regarding nutritional status, 47.8% were well nourished, 32.4% underweight and 19.7% malnourished. Baseline mean oxygen saturation was $93.4 \pm 3.2\%$. These demographic and clinical characteristics are summarized in **table 1**.

TABLE 1: Baseline demographic and clinical characteristics (n = 370)

Variable	n (%) / Mean \pm SD
Mean age (years)	7.1 \pm 2.6
Male	224 (60.5)
Female	146 (39.5)
Age <5 years	232 (62.7)
Age \geq 5 years	138 (37.3)
Urban residence	265 (71.6)
Rural residence	105 (28.4)
Well nourished	177 (47.8)
Underweight	120 (32.4)
Malnourished	73 (19.7)
Previous ARI	164 (44.3)
Antibiotics in last 3 days	109 (29.5)
Baseline SpO ² (%)	93.4 \pm 3.2

The mean baseline serum potassium before nebulization was 4.18 ± 0.46 mmol/L, which significantly decreased to 3.76 ± 0.49 mmol/L thirty minutes after salbutamol administration, showing a mean decline of 0.42 mmol/L ($p < 0.001$). These findings are shown in **table 2** and **fig 1**.

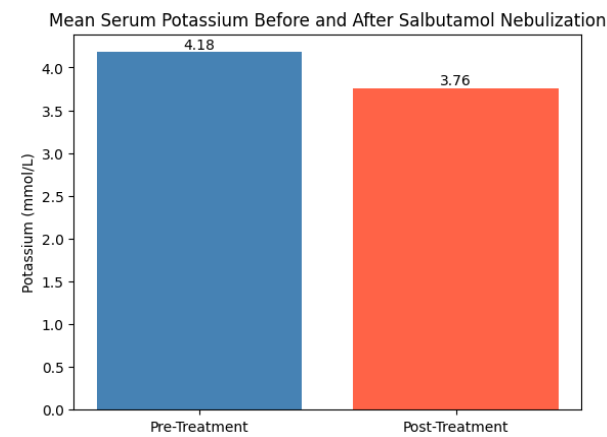


Fig 1: Mean serum potassium before and after salbutamol nebulization

TABLE 2: Serum potassium before and after salbutamol nebulization

Parameter	Mean \pm SD	p-value
Baseline Serum K ⁺ (mmol/L)	4.18 \pm 0.46	
Post-Nebulization Serum K ⁺ (mmol/L)	3.76 \pm 0.49	<0.001
Mean Decline (mmol/L)	0.42	

*p values <0.05 is considered statistically significant

Severity stratification of hypokalemia demonstrated that most cases were mild and transient. Among the 103 children who developed hypokalemia, 71 (68.9%) had mild hypokalemia (3.0–3.4 mmol/L), 26 (25.2%) had moderate hypokalemia (2.5–2.9 mmol/L), and 6 (5.8%) developed severe hypokalemia (<2.5 mmol/L). **table 3**.

TABLE 3: Severity of hypokalemia (n = 370)

Severity	Potassium Level	n (%)
Mild	3.0–3.4 mmol/L	71 (68.9)
Moderate	2.5–2.9 mmol/L	26 (25.2)
Severe	<2.5 mmol/L	6 (5.8)

The overall frequency of hypokalemia following nebulization was 27.8% (n = 103). Hypokalemia was significantly more frequent among children aged <5 years than \geq 5 years (32.4% vs 21.7%; $p=0.01$). Children receiving the higher salbutamol dose (5 mg) had a significantly greater frequency of hypokalemia than those receiving 2.5 mg (35.6% vs 22.9%; $p = 0.003$). Malnourished children had the highest hypokalemia occurrence (39.1%) compared to well-nourished children (18.8%; $p < 0.001$). These subgroup comparisons are presented in Table 4 and graphically depicted in **fig 2**.

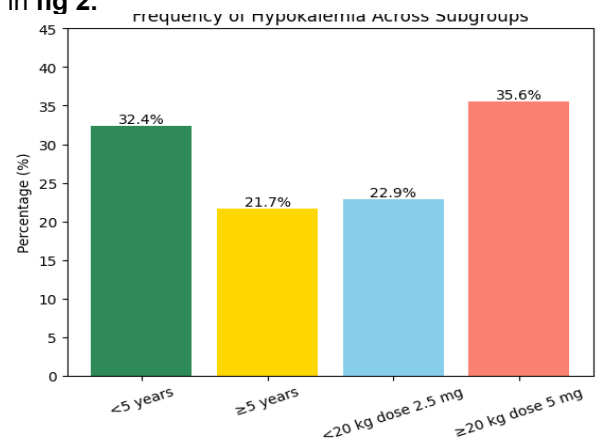


Fig 2: Frequency of hypokalemia across subgroups

TABLE 4: Frequency of hypokalemia across subgroups

Group	Hypokalemia n (%)	p-value
Overall	103 (27.8)	
Age <5 years	75 (32.4)	0.01
Age ≥5 years	28 (21.7)	
<20 kg (2.5 mg dose)	54 (22.9)	0.003
≥20 kg (5 mg dose)	49 (35.6)	
Well-nourished	34 (18.8)	<0.001

Malnourished	32 (39.1)
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*p values <0.05 is considered statistically significant

Multivariate logistic regression identified age <5 years (AOR 1.92; 95% CI: 1.18–3.11; p = 0.008), higher Salbutamol dose (AOR 2.04; 95% CI: 1.29–3.22; p = 0.002), and malnutrition (AOR 2.57; 95% CI: 1.56–4.21; p < 0.001) as significant independent predictors of hypokalemia **table 5**.

TABLE 5: Predictors of hypokalemia (multivariate regression)

Variable	Adjusted OR	95% CI	p-value
Age <5 years	1.92	1.18–3.11	0.008
Male sex	1.11	0.70–1.74	0.64
Urban residence	0.91	0.58–1.44	0.69
Baseline SpO ₂	0.97	0.91–1.03	0.28
Higher salbutamol dose	2.04	1.29–3.22	0.002
Malnutrition	2.57	1.56–4.21	<0.001

*p values <0.05 is considered statistically significant

Among children who developed hypokalemia, 82 (79.6%) remained asymptomatic, while 21 (20.4%) reported mild symptoms such as generalized weakness, fatigue, or muscle cramps. Only 16 children (15.5%) required potassium supplementation, and all showed prompt biochemical correction.

DISCUSSION

Salbutamol is well accepted as first line bronchodilator for the treatment of children with asthma who are hypokalemic due to its strong effect as a β_2 -adrenergic receptor agonist, but via stimulation of cellular Na/K-ATPase channels initiates intracellular potassium influxes, which in turn lowers extracellular potassium concentration and causes hypokalemia.⁵ This study has shown a statistically significant fall in serum potassium after a standardized salbutamol nebulization and recorded in 27.8% of the children post-treatment hypokalemia. This finding further supports previous pharmacologic and clinical evidence for measurable electrolyte shifts produced by β_2 -agonists, even in patients with mild asthma exacerbations.⁶

Some similar findings are reflected in studies from Pakistan. Post-salbutamol hypokalemia has been observed at the Karachi and Lahore pediatric emergency departments in approximately 20–35%

with an average reduction of between 0.3 and 0.5 mmol/l, figures that are comparable to our mean drop (0.42 mmol/l). Local clinical audits have identified this as a poorly recognized adverse effect in busy ED practice where electrolyte monitoring is frequently neglected unless mandated by clinical indication. Nevertheless, in contrast to several regional reports including patients with moderate-to-severe asthma, ICU admission or adjunctive steroid therapy the present study deliberately included only mild asthma exacerbations so that most of biochemical changes observed could be attributed to salbutamol alone diminishing confounding factors.^{7,8}

International evidence provides robust corroboration. Landmark placebo-controlled UK studies showed repeated salbutamol doses reduced serum potassium within 1–3 hour; hypokalemia (25–35% of children).⁹ Presumably, the decrease in mean serum potassium by 0.3 to 0.6 mmol/L described in randomized pediatric trials (conducted in Europe and North America) is similar to that observed here.¹⁰ The multicenter Canadian, Australian and US trials, conducted in different settings and with different designs, consistently demonstrated that higher cumulative exposure, continuous nebulization or frequent dosing are associated with an increased risk of hypokalemia.¹¹

In addition, a number of extensive pharmacovigilance reviews in industrialized countries have recognized that beta-agonist-induced hypokalemia is an established, predictable, and dose-related physiological effect.

The observation that hypokalemia was 3.8 times more common and severe in younger children is biologically plausible and consistent with previous reports. Clinical and physiologic research conducted in Pakistani children have indicated that preschoolers might exhibit increased β -receptor sensitivity and reduced reserve capacity for electrolytes.¹² The international pediatric pharmacology literature compares age-category as a modifier; smaller total potassium pools, high metabolic turnover, and proportionately greater exposure to β 2-agonists for weight in young children are considered major reasons why susceptibility increases with younger age.¹³

Dose dependency observed in this study as higher dose of salbutamol (5 mg nebulized) tended to cause redness more than its lower dose worldwide, even our local and international literature confirmed the same pattern. The British Thoracic Society (BTS/SIGN) guidelines, Global Initiative for Asthma (GINA), and American Academy of Pediatrics warn against high-dose or frequent β 2-agonist use, which may lead to transient biochemical hypokalemia.¹⁴ Dose-response effects: Multiple controlled trials have shown that the higher the dose of NaCl, the larger is the shift of electrolyte.¹⁵ The findings of this study further support these recommendations in a Pakistani population and emphasize rational dosing with particular reference to pediatric populations with low body weight.

Dietary intake was another determinant of significance that emerged. Hypokalemia prevalence was significantly higher among malnourished children.¹⁶ This observation has considerable clinical implications in undernourished population of Pakistan. While few Pakistani studies have systematically looked at this relationship, national nutrition surveys and pediatric clinical experience have long recognized electrolyte imbalance in malnourished children.¹⁷ Studies from outside of India in South Asian and African children also reveal increased vulnerability to drug-induced hypokalemia among malnourished children, due to diminished baseline potassium

stores, distortion of muscle mass distribution within the body and defective intracellular buffering.¹⁸

Although there was biochemical decrement, only few patients needed potassium supplementations and, in our cohort, no serious arrhythmias or mortalities were encountered. This is consistent with Pakistani emergency medicine literature and in line with many other international studies where salbutamol induced hypokalemia is primarily transient and infrequently causes clinical disaster in otherwise well children.¹⁹ However, rare international publications reported on severe arrhythmias, conduction disturbances (or even asystole) when there was a combination of additional risk factors such as dehydration or concomitant diuretic therapy or severe hypoxia. Although most of pediatric patients tolerate salbutamol without adverse effects, we should not be relaxed particularly in the presence of more than one risk factor.²⁰

Taken together these findings are concordant with Pakistani and international studies as well, emphatically supporting that hypokalemia after nebulized salbutamol is a dose dependent, pharmacologically mediated, age sensitive and nutrition influenced phenomenon.²¹ This study provides important regional evidence for the extent of this effect, especially in mild asthma exacerbations and under standardized dosing with the absence of confounders, helping to clarify clinical presentations in day-to-day pediatric ED settings.

Despite these findings, several limitations must be acknowledged. First, the study was conducted at a single center, which may limit generalizability. Second, routine electrocardiographic (ECG) monitoring was not performed, and therefore subclinical arrhythmias potentially associated with hypokalemia could not be evaluated. Since cardiac arrhythmia is a clinically important consequence of significant hypokalemia, the absence of systematic ECG monitoring represents an important limitation. Third, potassium measurements were performed at a single post-treatment time point, preventing evaluation of the duration of electrolyte changes.

CONCLUSION

Nebulized salbutamol produced a significant but generally mild reduction in serum potassium levels,

with biochemical hypokalemia observed in 27.8% of children treated for mild asthma exacerbation. Most cases were mild and clinically asymptomatic. Younger age, higher salbutamol dose, and malnutrition were significant predictors. These findings suggest that while salbutamol-induced hypokalemia is usually transient, monitoring may be warranted in high-risk children, particularly those who are young, malnourished, or receiving higher cumulative doses.

Source of funding: None

Conflict of interest: None

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Author's Contribution

S: Proposed topic, basic study design, methodology and manuscript writing, Collected data and did the manuscript writing

WJ: Collected data and did the manuscript writing

MS: Collected data and did the manuscript writing

AS: Collected data and did the manuscript writing

HS: Did the statistical analysis, interpretation, results section and manuscript review

Y: Did the statistical analysis, interpretation, results section and manuscript review

All the authors have approved the final manuscript draft and accept the responsibility of research integrity.