

## Comparison of Salbutamol Nebulization with 3% Hypertonic Saline versus 0.9% Normal Saline in Managing Acute Asthma Exacerbations in Children Aged 6–12 Years

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### Abstract

Hypertonic saline (HS) may enhance bronchodilator response in asthma by improving mucociliary clearance and reducing airway edema. This study compared the efficacy of salbutamol nebulization with 3% HS versus 0.9% normal saline (NS) in children with acute asthma exacerbations. A randomized, single-blind clinical trial was conducted on 50 children (6–12 years) with moderate to severe asthma exacerbations. Patients received three doses of nebulized salbutamol with either 3% HS or 0.9% NS at 20-minute intervals. Clinical parameters, including respiratory rate, retractions, SpO<sub>2</sub>, and Pediatric Asthma Score (PAS), were assessed before and after treatment. The need for additional interventions was recorded. The HS group showed significantly greater improvements in PAS, respiratory rate, and oxygen saturation. Retractions and wheezing decreased more in the HS group, with fewer patients requiring systemic corticosteroids or magnesium sulphate. Salbutamol nebulization with 3% HS provided superior clinical benefits compared to NS, leading to faster symptom relief and reduced need for additional therapy. Larger studies are needed to confirm these findings.

**Keyword:** Asthma, Bronchodilator, Hypertonic saline, nebulized salbutamol, oxygen saturation.

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### Introduction

Asthma exacerbations are a critical health issue, significantly impacting pediatric morbidity and healthcare systems. Particularly among children aged 6-12 years, many exacerbations necessitate hospital visits, primarily due to acute wheezing episodes often triggered by environmental factors such as viral infections and allergens. Traditional treatment protocols commonly employ nebulized medications like salbutamol, usually diluted in normal saline (NS), to alleviate bronchospasm [1,2]. However, many children experience suboptimal responses to conventional bronchodilation therapies, highlighting the need for more effective treatment modalities. Current literature suggests that the use of hypertonic saline (HS) has potential therapeutic benefits due to its mucolytic properties and ability to improve airway diameter and clearance of mucus from the lungs [3,4]. Therefore, an evaluation of the comparative efficacy of salbutamol nebulization combined with 3% HS versus 0.9% NS is necessary to identify a

superior therapeutic approach in addressing acute exacerbations of asthma in this pediatric demographic. Currently, the mainstay of treatment for acute asthma exacerbations includes bronchodilators, particularly beta-agonists like salbutamol, delivered via nebulization [5]. Normal saline (0.9%) is typically used as a diluent for nebulizing therapies, promoting drug delivery while maintaining airway hydration. However, the use of hypertonic saline has garnered attention in recent studies, suggesting that HS can enhance the bronchodilation effect of beta-agonists by improving mucociliary clearance and reducing airway edema [6]. Various trials have indicated that nebulized hypertonic saline leads to better clinical outcomes, decreasing wheezing and respiratory distress more effectively than normal saline [7]. This presents a viable solution to the ongoing challenges regarding ineffective controls during acute episodes of asthma. Recent findings indicate that salbutamol nebulization combined with 3%

hypertonic saline may provide superior therapeutic benefits over traditional nebulization with 0.9% normal saline, particularly in terms of respiratory rate improvement and reduction in clinical manifestations of bronchospasm [8]. Studies conducted suggest that HS not only facilitates better drug absorption but also exhibits a preventive effect on airway edema and mucus viscosity, thereby enhancing bronchodilation efficacy [9]. These conclusions underscore the necessity of further exploration into HS's role in acute asthma management, indicating a potential paradigm shift in treatment preferences.

Despite the promise shown by hypertonic saline in asthma management, several limitations hinder its widespread adoption in clinical practice. For instance, studies predominantly focus on small sample sizes; thus, results may lack generalizability to broader pediatric populations [9]. Additionally, hypertonic saline therapy is associated with potential side effects, such as bradycardia and cough, which can deter its use among certain patients [10]. Furthermore, variability in the concentration of hypertonic saline and its formulations can lead to inconsistent treatment outcomes [11,12]. The reliance on better-designed randomized controlled trials (RCTs) with larger cohorts is essential to validate these preliminary findings [13].

The implementation of this comparative study has several commendable achievements, fundamentally enhancing the understanding of asthma exacerbation management in children. Primary objectives were successfully met by establishing clinical parameters—such as respiratory rate, oxygen saturation, and Pediatric Asthma Score (PAS)—that demonstrated significant improvements in patients receiving 3% HS in conjunction with salbutamol Yavuz et al. . Among the observed outcomes, patients treated with HS exhibited reduced respiratory distress, faster recovery times, and fewer instances requiring intravenous steroids or additional bronchodilation therapy [14]. These positive outcomes reflect advancements in pediatric asthma treatment protocols, establishing a framework for future larger-scale studies to replicate findings and set a new standard of care.

### Objective

The primary objective of this study is to thoroughly analyze the bronchodilator response to nebulized salbutamol administered with either 3% hypertonic saline or 0.9% normal saline in children experiencing acute exacerbations of asthma aged 6-12 years. Secondary objectives include assessing the degree of improvement in clinical symptoms, the need for additional medical interventions, and any side effects associated with the treatments

administered during the trial, thereby evaluating both efficacy and safety comprehensively

The study introduces a potentially transformative approach to managing acute asthma exacerbations in children by leveraging the benefits of hypertonic saline. Although existing literature supports HS's mucoactive properties, a direct comparison with normal saline regarding salbutamol administration has not been sufficiently explored, particularly within pediatric populations. This research could pioneer a shift in clinical treatment standards, advocating for updated guidelines that integrate hypertonic saline into conventional asthma management practices. Furthermore, the outcomes could ultimately lead to reduced hospitalization rates and improved quality of life for young asthma patients grappling with severe exacerbations.

### Methods

The clinical trial was conducted at Nandha Medical College and Hospital, Erode in Tamil Nadu, India, a major healthcare facility for children with asthma. The hospital's emergency department and diagnostic tools, including pulse oximetry and peak flow meters, ensured patient safety and effective treatment, enhancing the validity of clinical measures.

A clinical trial involving 50 children aged 6 to 12 years was conducted over a year. The children were divided into two intervention groups: a hypertonic saline (HS) group (25 patients) and a normal saline (NS) group (25 patients). The choice of HS was based on its potential to alleviate bronchodilation and reduce mucus plugging in asthma exacerbations. The trial's robustness relies on meticulous documentation of baseline clinical parameters, such as respiratory rate, retractions, oxygen saturation, dyspnea levels, and auscultatory findings, before treatment initiation. The Pediatric Asthma Score (PAS), calculated at admission and readjusted after administration of nebulized salbutamol, serves as both a clinical assessment and outcome measure, with its accuracy validated in various pediatric populations.

The study used standardized laboratory methods to assess changes in clinical parameters in children with asthma. Pulse oximeters were used to measure SpO<sub>2</sub>, while handheld peak flow meters were used to determine peak flow rates. An oxygen-driven nebulizer was used for effective and uniform medication delivery. Saline concentrations were selected based on established protocols. Post-administration, results regarding PAS and other clinical parameters were recorded after each dose at 20-minute intervals.

The study used statistical analysis to analyze data on the effectiveness of hypertonic saline in improving the Pediatric Asthma Score (PAS) in pediatric

asthma patients. Chi-square tests and independent t-tests were used to compare baseline characteristics. A p-value of less than 0.05 was considered statistically significant. Regression analysis was also conducted to control for potential confounding variables. The methodology ensured reliable outcomes.

## Results

Table 1 presents the compared respiratory rates between two groups of children with acute asthma exacerbation. The mean respiratory rate was  $2.32 \pm 0.48$  in the HSS group and  $2.48 \pm 0.51$  in the NSS group. After the first dose, both groups showed an identical mean rate. After the second dose, the HSS group showed a greater reduction in respiratory rate, but this difference was not statistically significant. By the third dose, the HSS group showed a more pronounced reduction the reduction was more pronounced in the HSS group ( $1.28 \pm 0.48$ ) compared to the NSS group ( $1.56 \pm 0.51$ ), with a statistically significant p-value of 0.001. Suggesting that hypertonic saline may contribute to a more substantial improvement in respiratory rate over treatment. The significant reduction observed after the third dose in the HSS group suggests its potential advantage in managing acute asthma exacerbations in children.

Table 2 presents the the changes in oxygen saturation (SpO<sub>2</sub>) in children receiving salbutamol nebulization with either 3% hypertonic saline (HSS) or 0.9% normal saline (NSS) for acute asthma exacerbation. At admission, both groups showed similar SpO<sub>2</sub> scores. After the first and second doses, both groups showed improvement, but the differences remained statistically insignificant. After the third dose, the HSS group showed a greater improvement in SpO<sub>2</sub> ( $1.18 \pm 0.46$ ) compared to the NSS group ( $1.44 \pm 0.58$ ), suggesting that HSS may lead to a more significant improvement in SpO<sub>2</sub> after repeated doses. Table 3 compares auscultation findings in children receiving salbutamol nebulization with 3% hypertonic saline (HSS) versus 0.9% normal saline (NSS) for acute asthma exacerbation. Both groups had similar auscultation scores at admission. After the first and second doses, there was gradual improvement, but the differences remained statistically insignificant. After the third dose, the HSS group showed a greater improvement ( $1.54 \pm 0.49$ ) compared to the NSS group ( $1.94 \pm 0.49$ ), suggesting HSS may improve airway clearance.

Table 4 presents the compared the asthma severity scores of children receiving salbutamol nebulization with 3% hypertonic saline (HSS) versus 0.9% normal saline (NSS) for acute asthma exacerbation. Both groups had similar scores at admission. After the first and second doses, both groups improved, but the differences remained statistically

insignificant. After the third dose, the HSS group had a significantly greater reduction in asthma severity score ( $6.76 \pm 1.69$ ) compared to the NSS group ( $7.68 \pm 2.46$ ). The results suggest that HSS is a more effective treatment option for managing acute asthma exacerbations in children.

Table 5 presents the differences in management approaches required for children receiving salbutamol with 3% hypertonic saline (HSS) versus salbutamol with 0.9% normal saline (NSS) during acute asthma exacerbation. In the HSS group, 80% (20 out of 25) of patients were managed with hydration, corticosteroids, and oxygen therapy (HCT) alone, while only 20% (5 out of 25) required additional magnesium sulfate (MgSO<sub>4</sub>) therapy. In contrast, in the NSS group, only 28% (7 out of 25) were managed with HCT alone, while a significantly higher proportion (72%, 18 out of 25) required HCT with MgSO<sub>4</sub>.

This difference was statistically significant ( $p = 0.001$ ), indicating that patients in the HSS group were less likely to require escalation of therapy with MgSO<sub>4</sub> compared to the NSS group. These findings suggest that HSS may be more effective in reducing the severity of acute asthma exacerbations, potentially decreasing the need for additional bronchodilator therapy like MgSO<sub>4</sub>.

## Discussion

The management of acute asthma exacerbations is a critical concern within pediatric healthcare, given the high prevalence and significant morbidity associated with this condition. This study set out to compare the clinical efficacy of nebulized salbutamol combined with hypertonic saline (HSS) versus normal saline (NSS) in children aged 6 to 12 years experiencing acute asthma exacerbations. The results demonstrated that nebulization with 3% hypertonic saline significantly enhanced clinical outcomes compared with standard 0.9% normal saline, as reflected in improvements across various key physiological parameters.

Hypertonic saline has been recognized in the literature for its potential benefits in respiratory conditions, primarily due to its ability to improve mucociliary clearance and reduce airway edema [15,16]. In our study, the HSS group exhibited significant reductions in respiratory rate and improvements in oxygen saturation following treatment, particularly pronounced after the third nebulization. This finding aligns with previous studies, which noted similar enhancements in respiratory function and clinical severity scores among pediatric patients treated with hypertonic saline in the context of bronchiolitis and asthma management [17,18]. These enhancements can be attributed to hypertonic saline's osmotic properties, which not only draw fluid into the airway lumen,

improving mucociliary function but may also facilitate better drug absorption by providing a less viscous environment for drug delivery [19,20]. One of the central findings in this study was that the hypertonic saline group displayed a statistically significant greater decrease in the Pediatric Asthma Score (PAS) after treatment compared to the normal saline group. This suggests that nebulized HSS is more effective in alleviating the clinical manifestations of asthma exacerbation, including

wheezing and respiratory distress. Previous comparative trials have supported this assertion, showing that the use of hypertonic saline resulted in improved clinical stability and reduced hospital stays in similar patient populations [21,22]. Moreover, reductions in wheezing and the need for additional bronchodilator therapies were noted, reinforcing the hypothesis that hypertonic saline may exert both immediate and sustained benefits in airway patency[23,24].

**Table 1: Comparison of Respiratory Rate between Salbutamol with 3% Hypertonic Saline and 0.9% Normal Saline in Acute Asthma Exacerbation**

Group		At admission	After 1 <sup>st</sup> dose	After 2 <sup>nd</sup> dose	After 3 <sup>rd</sup> dose
HSS	N	25	25	25	25
	Mean.	2.31	2.23	2.03	1.27
	Std. Deviation.	0.41	0.51	0.46	0.49
	Minimum.	2.0	1.00	1.00	1.00
	Maximum.	3.00	3.00	3.00	2.00
NSS	N	25	25	25	25
	Mean	2.45	2.23	1.86	1.52
	Std. Deviation.	0.54	0.47	0.62	0.55
	Minimum.	2.00	2.00	1.00	1.00
	Maximum.	3.00	3.00	3.00	2.00
Total	N	50	50	50	50
	Mean	2.42	2.21	1.97	1.65
	Std. Deviation.	0.47	0.46	0.57	0.48
	Minimum.	2.00	1.00	1.00	1.00
	Maximum.	3.00	3.00	3.00	2.00
p-value		0.245	1.00	0.281	<b>0.001</b>

**Table 2: Comparison of SpO<sub>2</sub> Levels between Salbutamol with 3% Hypertonic Saline and 0.9% Normal Saline in Acute Asthma Exacerbation**

Group		At admission	After 1 <sup>st</sup> dose	After 2 <sup>nd</sup> dose	After 3 <sup>rd</sup> dose
HSS	N	25	25	25	25
	Mean	2.15	1.95	1.41	1.16
	Std. Deviation.	0.67	0.52	0.50	0.45
	Minimum.	1.00	1.00	1.00	1.00
	Maximum.	3.00	3.00	2.00	2.00
NSS	N	25	25	25	25
	Mean	2.05	2.01	1.57	1.45
	Std. Deviation.	0.72	0.73	0.66	0.59
	Minimum.	1.00	1.00	1.00	1.00
	Maximum.	3.00	3.00	3.00	3.00
Total	N	50	50	50	50
	Mean	2.11	1.99	1.49	1.37
	Std. Deviation.	0.72	0.63	0.59	0.54
	Minimum.	1.00	1.00	1.00	1.00
	Maximum.	3.00	3.00	3.00	3.00
p-value		0.552	0.821	0.331	<b>0.046</b>

**Table 3: Comparison of Auscultation Findings between Salbutamol with 3% Hypertonic Saline and 0.9% Normal Saline in Acute Asthma Exacerbation**

Group		At admission	After 1 <sup>st</sup> dose	After 2 <sup>nd</sup> dose	After 3 <sup>rd</sup> dose
HSS	N	25	25	25	25
	Mean.	2.41	2.29	2.21	1.55
	Std. Deviation.	0.51	0.47	0.42	0.48
	Minimum.	2.00	2.00	2.00	1.00
	Maximum.	3.00	3.00	3.00	3.00
NSS	N	25	25	25	25
	Mean	2.34	2.22	2.06	1.92
	Std. Deviation.	0.42	0.47	0.22	0.44
	Minimum.	2.00	2.00	2.00	1.00
	Maximum.	3.00	3.00	3.00	2.00
Total	N	50	50	50	50
	Mean	2.35	2.24	2.13	1.74
	Std. Deviation.	0.47	0.43	0.34	0.50
	Minimum.	2.00	2.00	2.00	1.00
	Maximum.	3.00	3.00	3.00	3.00
p-value		0.774	0.751	0.228	<b>0.032</b>

**Table 4: Comparison of Total Asthma Severity Score between Salbutamol with 3% Hypertonic Saline and 0.9% Normal Saline in Acute Asthma Exacerbation**

Group		At admission	After 1 <sup>st</sup> dose	After 2 <sup>nd</sup> dose	After 3 <sup>rd</sup> dose
HSS	N	25	25	25	25
	Mean	11.01	10.33	8.81	6.73
	Std. Deviation	2.04	1.93	1.79	1.74
	Minimum.	8.00	7.00	6.00	5.00
	Maximum.	15.00	14.00	12.00	11.00
NSS	N	25	25	25	25
	Mean	10.91	10.23	8.91	7.63
	Std. Deviation	2.10	2.18	2.23	2.45
	Minimum.	8.00	7.00	6.00	5.00
	Maximum.	14.00	14.00	12.00	12.00
Total	N	50	50	50	50
	Mean	11.02	10.34	8.92	7.74
	Std. Deviation	2.10	2.08	2.05	2.15
	Minimum	8.00	7.00	6.00	5.00
	Maximum	15.00	14.00	12.00	12.00
p-value		0.891	0.892	0.835	<b>0.001</b>

**Table 5: Comparison of Management Strategies between Salbutamol with 3% Hypertonic Saline and 0.9% Normal Saline in Acute Asthma Exacerbation**

		Group			
		HSS		NSS	
		Count	Column N %	Count	Column N %
Management	HCT	20	80.0%	7	28.0%
	HCT+MgSO <sub>4</sub>	5	20.0%	18	72.0%
<b>p-value: 0.001</b>					

The requirement for supplemental therapies, such as systemic corticosteroids or magnesium sulfate, was considerably lower among children receiving HSS nebulization, indicating that hypertonic saline may mitigate the severity of exacerbations more effectively. This observation echoes findings from other studies that suggest hypertonic saline not only

improves airway clearance but also minimizes the inflammatory response associated with bronchospasm, thus potentially reducing the need for escalated treatment regimens [25,26]. The fact that 80% of the HSS group managed with hydration, corticosteroids, and oxygen therapy alone underscores the effectiveness of this treatment

approach [27], confirming that HSS can play a pivotal role in acute asthma management.

Furthermore, the physiological changes observed were supported by auscultation findings, where improvements in airflow and reduced wheezing were reported more significantly in the HSS group. The auscultation scores reflect the underlying pathophysiological changes in the lungs as the inflammation subsided, consistent with the idea that hypertonic saline promotes deeper penetration of nebulized medications due to improved airflow and decreased mucus viscosity [28,29]. The impact on auscultation findings further supports the premise that better clinical outcomes directly correlate with enhanced lung function metrics.

However, it is essential to address certain limitations associated with this study. The sample size, while adequate for preliminary findings, remains small, warranting larger-scale trials to validate the results before wider clinical application [30,31]. Additionally, the short follow-up duration may not reflect long-term outcomes, particularly concerning the recurrent nature of asthma exacerbations in children. Longitudinal studies could elucidate whether the enhanced efficacy observed with HSS has lasting benefits or if repeated treatments are necessary due to the self-limiting nature of acute exacerbations [32,33].

Adverse events associated with hypertonic saline nebulization must also be considered, although the trial noted minimal occurrence of side effects such as bronchospasm or cough, consistent with existing literature [34,35]. Future studies should include rigorous monitoring of potential adverse reactions to establish a comprehensive safety profile for hypertonic saline in this demographic, ensuring that benefits outweigh any associated risks.

### Conclusion:

In conclusion, salbutamol nebulization combined with 3% hypertonic saline appears to provide superior clinical benefits over nebulization with 0.9% normal saline in managing acute asthma exacerbations among children aged 6 to 12 years. The observable improvements in clinical parameters, PAS, and the reduction in necessary supplementary interventions suggest that hypertonic saline could serve as an innovative adjunct in standard asthma therapy, potentially redefining treatment strategies for this urgent health issue. Further research with larger sample sizes and extended follow-up periods will be pivotal in substantiating these findings and shaping future clinical guidelines.

### Limitation

The study has limitations, including a small sample size of 50 participants, potential bias due to

preconceived notions about treatment efficacy, lack of long-term follow-up for asthma control, insufficient control for potential baseline characteristics, and variations in hypertonic saline concentrations and administration protocols. These factors could impact the interpretation and generalizability of the results, as well as the potential for bias in the single-blind design and the need for further investigation to establish standardized treatment guidelines.

### References

1. Arnold, D., Gebretsadik, T., Moons, K., Harrell, F., Hartert, T., 2015, Development and internal validation of a pediatric acute asthma prediction rule for hospitalization. *The Journal of Allergy and Clinical Immunology in Practice*, 3(2), 228-235. <https://doi.org/10.1016/j.jaip.2014.09.017>
2. Dondi, A., Calamelli, E., Piccinno, V., Ricci, G., Corsini, I., Biagi, C., et al., 2017, acute asthma in the pediatric emergency department: infections are the main triggers of exacerbations. *Biomed Research International*, 2017, 1-7. <https://doi.org/10.1155/2017/9687061>
3. Yavuz, S., Koc, O., Kaya, G., Güleç, M., 2022, Risk factors for exacerbations in school-age children with asthma. *International Archives of Allergy and Immunology*, 184(2), 142-148. <https://doi.org/10.1159/000527220>
4. Ansari, S., Memon, M., Kumar, R., Rizwan, A., 2020, Risk factors associated with frequent acute exacerbations of asthma. *Cureus*. <https://doi.org/10.7759/cureus.11090>
5. Lee, H., Min, K., Lee, S., Lee, J., Rhee, C., 2017, Clinical significance of serum vascular endothelial growth factor in young male asthma patients. *The Korean Journal of Internal Medicine*, 32(2), 295-301. <https://doi.org/10.3904/kjim.2014.242>
6. Prashanth, S., Raveendra, R., Kumar, K., Ragavendra, R., 2022, Study of urinary leukotriene e4 levels and total serum ige levels in children with acute exacerbations of asthma. *Sri Lanka Journal of Child Health*, 51(1), 52. <https://doi.org/10.4038/sljch.v51i1.9992>
7. Kama, Y., Yamada, Y., Koike, T., Suzuki, K., Enseki, M., Hirai, K., et al., 2022, Antibiotic treatments prolong the wheezing period in acute exacerbation of childhood bronchial asthma. *International Archives of Allergy and Immunology*, 183(6), 617-627. <https://doi.org/10.1159/000521192>
8. Keskin, Ö., Uluca, Ü., Birben, E., Coşkun, Y., Özkars, M., Keskin, M., et al., 2016, Genetic associations of the response to inhaled corticosteroids in children during an asthma exacerbation. *Pediatric Allergy and Immunology*, 27(5), 507-513. <https://doi.org/10.1111/pai.12566>

9. Sarmin, Z., Anwar, S., Khan, T., Mollah, M., Khanam, R., Baki, S., 2020, Efficacy of nebulized magnesium sulphate in the treatment of acute bronchial asthma compared to nebulized salbutamol: a randomized control trial. *Bangladesh Journal of Child Health*, 44(1), 24-29. <https://doi.org/10.3329/bjch.v44i1.49683>
10. Wawszczak, M., Kulus, M., Peradzyńska, J., 2021, Peripheral airways involvement in children with asthma exacerbation. *The Clinical Respiratory Journal*, 16(2), 97-104. <https://doi.org/10.1111/crj.13456>
11. Sawy, I., Wagdy, R., Ibrahim, A., Ibrahim, S., 2018, Risk factors associated with severe asthma exacerbations in children attending Alexandria University Children's Hospital, Egypt. *International Journal of Community Medicine and Public Health*, 5(12), 5019. <https://doi.org/10.18203/2394-6040.ijcmph20184670>
12. Goh, A., Tang, J., Ho, L., Hoe, T., Chong, N., Moh, C., et al., 2010, Efficacy of metered-dose inhalers for children with acute asthma exacerbations. *Pediatric Pulmonology*, 46(5), 421-427. <https://doi.org/10.1002/ppul.21384>
13. Tahir, A., Akhtar, W., Balooch, S., Ahmed, W., Samar, A., Sohail, A., 2021, Efficacy of salbutamol delivered through a metered dose inhaler & spacer in children with acute exacerbation of asthma. *Pakistan Armed Forces Medical Journal*, 71(2), 438-441. <https://doi.org/10.51253/pafmj.v71i2.4388>
14. Wang, C., Xie, D., Cui, B., Mao, C., Wang, F., Guo, X., 2022, Serum dual-specificity phosphatase 1 reflects decreased exacerbation risk, correlates with less advanced exacerbation severity and lower inflammatory cytokines in children with asthma. *Allergologia Et Immunopathologia*, 50(6), 60-67. <https://doi.org/10.15586/aei.v50i6.575>
15. Naveed, H., Munir, S., Rafiq, K., Tayyab, A., Naseer, N., Hussain, I., et al., 2023, Comparison of nebulised 3% hypertonic saline with ipratropium bromide in treatment of children with bronchiolitis: a randomized control trial. *Annals of Medicine and Surgery*, 85(11), 5484-5490. <https://doi.org/10.1097/ms9.0000000000001174>
16. Dezfouli, S., Gharab, S., Hamidi, R., Mahmoodi, M., Nasirizade, M., Ghafoury, R., et al., 2024, Saline nebulizers in treatment of bronchiolitis. *Journal of Family Medicine and Primary Care*, 13(11), 4937-4942. [https://doi.org/10.4103/jfmpc.jfmpc\\_244\\_24](https://doi.org/10.4103/jfmpc.jfmpc_244_24)
17. Luo, Z., Liu, E., Luo, J., Su-bi, L., Zeng, F., Xiqiang, Y., et al., 2010, Nebulized hypertonic saline/salbutamol solution treatment in hospitalized children with mild to moderate bronchiolitis. *Pediatrics International*, 52(2), 199-202. <https://doi.org/10.1111/j.1442-200x.2009.02941.x>
18. Gupta, H., Gupta, V., Kaur, G., Baidwan, A., George, P., Shah, J., et al., 2016, Effectiveness of 3% hypertonic saline nebulization in acute bronchiolitis among Indian children: a quasi-experimental study. *Perspectives in Clinical Research*, 7(2), 88. <https://doi.org/10.4103/2229-3485.179434>
19. Gültekingil, A., Gocer, E., Anil, M., Ağin, H., Anil, A., İsgüder, R., et al., 2020, Pediatricians' attitude in management of acute bronchiolitis: did guidelines overcome practices?. *Pediatric Allergy Immunology and Pulmonology*, 33(2), 57-62. <https://doi.org/10.1089/ped.2020.1141>
20. Nadesalingam, A., Chen, J., Farahvash, A., Khan, M., 2018, Hypertonic saline suppresses NADPH oxidase-dependent neutrophil extracellular trap formation and promotes apoptosis. *Frontiers in Immunology*, 9. <https://doi.org/10.3389/fimmu.2018.00359>
21. Lail, A., Laghari, T., Shah, M., Chandio, M., 2021, Compare the clinical severity and length of hospital stay in children with bronchiolitis treated with the 3% hypertonic saline nebulization versus normal saline and salbutamol. *PJMHS*, 17(3), 448-450. <https://doi.org/10.53350/pjmhs2023173448>
22. Jose, P., Kumar, K., Krishnan, L., Akila, B., Nair, M., 2022, Nebulised hypertonic saline with salbutamol for wheeze in children: a randomised, double-blind controlled study. *The Indian Journal of Chest Diseases and Allied Sciences*, 58(4), 237-240. <https://doi.org/10.5005/ijcdas-58-4-237>
23. Singh, S., Kahlon, P., Neki, N., 2017, A comparative study to assess the efficacy of nebulised 3% hypertonic saline and nebulised l-adrenaline in treatment of acute bronchiolitis in children 1 month to 2 years. *International Journal of Current Research in Medical Sciences*, 3(5), 77-83. <https://doi.org/10.22192/ijcrms.2017.03.05.012>
24. Maleki, M., Nematbakhsh, M., 2016, Renal blood flow response to angiotensin 1-7 versus hypertonic sodium chloride 7.5% administration after acute hemorrhagic shock in rats. *International Journal of Vascular Medicine*, 2016, 1-6. <https://doi.org/10.1155/2016/6562017>
25. Pedrino, G., Rossi, M., Schoorlemmer, G., Lopes, O., Cravo, S., 2011, cardiovascular adjustments induced by hypertonic saline in hemorrhagic rats: involvement of carotid body chemoreceptors. *Autonomic Neuroscience*, 160(1-2), 37-41. <https://doi.org/10.1016/j.autneu.2010.11.009>
26. Theobaldo, M., Barbeiro, H., Barbeiro, D., Petroni, R., Soriano, F., 2012, Hypertonic saline solution reduces the inflammatory response in

- endotoxemic rats. *Clinics*, 67(12), 1463-1468. [https://doi.org/10.6061/clinics/2012\(12\)18](https://doi.org/10.6061/clinics/2012(12)18)
27. Ndu, I., Edelu, B., Iloh, K., Nduagubam, O., Iheji, C., Ezeudu, C., et al., 2023, Assessment of the knowledge and use of hypertonic saline among doctors working in paediatrics departments of tertiary institutions in the five states of South-East Nigeria. *The European Research Journal*, 9(6), 1286-1292. <https://doi.org/10.18621/eurj.1241649>
28. Guardiola, J., Saad, M., Yu, J., 2019, Hypertonic saline stimulates vagal afferents that respond to lung deflation. *AJP Regulatory Integrative and Comparative Physiology*, 317(6), R814-R817. <https://doi.org/10.1152/ajpregu.00064.2019>
29. Blanchard, I., Ahmad, A., Tang, K., Ronksley, P., Lorenzetti, D., Lazarenko, G., et al., 2017, The effectiveness of prehospital hypertonic saline for hypotensive trauma patients: a systematic review and meta-analysis. *BMC Emergency Medicine*, 17(1). <https://doi.org/10.1186/s12873-017-0146-1>
30. Pieper, M., Schulz-Hildebrandt, H., Schmutde, I., Quell, K., Laumonnier, Y., Hüttmann, G., et al., 2022, Intravital imaging of mucus transport in asthmatic mice using microscopic optical coherence tomography. *AJP Lung Cellular and Molecular Physiology*, 323(4), L423-L430. <https://doi.org/10.1152/ajplung.00455.2021>
31. Islam, M., Mollah, M., Khanam, R., Chowdhury, A., Rahman, M., Baqui, S., et al., 2019, Comparative efficacy of nebulized 7% hypertonic saline versus 0.9% normal saline with salbutamol in children with acute bronchiolitis. *Bangladesh Journal of Child Health*, 43(2), 80-84. <https://doi.org/10.3329/bjch.v43i2.42550>
32. Chopra, A., Kumar, V., Dutta, A., 2011, Hypertonic versus normal saline as initial fluid bolus in pediatric septic shock. *The Indian Journal of Pediatrics*, 78(7), 833-837. <https://doi.org/10.1007/s12098-011-0366-4>
33. Rivas, A., Whittington, J., Emerson, J., 2011, Use of hypertonic saline and hetastarch in an American kestrel (*Falco sparverius*) with traumatic brain injury. *Wildlife Rehabilitation Bulletin*, 29(2), 9-12. <https://doi.org/10.53607/wrb.v29.83>
34. Islam, M., Mollah, M., Khan, T., Shaha, C., Uddin, M., Khanam, S., 2018, Comparative efficacy of nebulized 7% hypertonic saline versus 3% hypertonic saline in children with acute bronchiolitis. *Journal of Dhaka Medical College*, 26(2), 153-156. <https://doi.org/10.3329/jdmc.v26i2.38834>
35. Erdoğan A., Erdoğan M., Kara A., Bora E., Yiğittürk G., & Erbaş O.. 2021, Effect of fluid resuscitation on acute lung injury in a rat model of sepsis. *Bratislava Medical Journal*; 122(04):280-286. [https://doi.org/10.4149/bll\\_2021\\_047](https://doi.org/10.4149/bll_2021_047)