

2016

Does Nebulized Hypertonic Saline Solution Decrease Hospital Admission Rates When Compared to Nebulized Normal Saline in Children Less Than or Equal to 24 Months Old With Bronchiolitis?

Korie Alecxih

Philadelphia College of Osteopathic Medicine, korieal@pcom.edu

Follow this and additional works at: http://digitalcommons.pcom.edu/pa_systematic_reviews



Part of the [Respiratory Tract Diseases Commons](#)

Recommended Citation

Alecxih, Korie, "Does Nebulized Hypertonic Saline Solution Decrease Hospital Admission Rates When Compared to Nebulized Normal Saline in Children Less Than or Equal to 24 Months Old With Bronchiolitis?" (2016). *PCOM Physician Assistant Studies Student Scholarship*. 264.

http://digitalcommons.pcom.edu/pa_systematic_reviews/264

This Selective Evidence-Based Medicine Review is brought to you for free and open access by the Student Dissertations, Theses and Papers at DigitalCommons@PCOM. It has been accepted for inclusion in PCOM Physician Assistant Studies Student Scholarship by an authorized administrator of DigitalCommons@PCOM. For more information, please contact library@pcom.edu.

Does nebulized hypertonic saline solution decrease hospital admission rates when compared to nebulized normal saline in children less than or equal to 24 months old with bronchiolitis?

Korie Alexih, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences—Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 18th, 2015

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not nebulized hypertonic saline solution reduces hospital admission rates when compared to nebulized normal saline solution in children less than or equal to 24 months of age diagnosed with acute bronchiolitis in the emergency department setting.

STUDY DESIGN: Systematic review of three randomized, double-blind, placebo controlled trials in the English language all published in 2014.

DATA SOURCES: Data sources obtained for this review were articles published in peer-reviewed journals found using PubMed Database.

OUTCOMES MEASURED: The outcome measured was hospital admission rate. Hospital admission rate is calculated as the number of patients requiring inpatient hospitalization divided by the total number of patients randomized.

RESULTS: Three double-blind randomized, controlled trials were included and analyzed in this review. The study by Wu et al showed a statistically significant reduction ($p=0.01$) in hospital admission rate with the administration of nebulized hypertonic saline compared to nebulized normal saline with a number needed to treat (NNT) of 9. The second study by Jacobs et al showed a decrease in admission rate with hypertonic saline that was not statistically significant compared to control. The third study by Florin et al showed a slight increase in hospital admission rate with the use of nebulized hypertonic saline compared to control that was not statistically significant.

CONCLUSIONS: The results of the randomized, controlled trials were conflicting. Future study is warranted to evaluate the efficacy of hypertonic saline in reducing hospital admission rate.

KEY WORDS: Bronchiolitis; nebulized hypertonic saline; admission rate

INTRODUCTION

Bronchiolitis is a common viral infection of the lower respiratory tract that is responsible for substantial morbidity in children under two years of age. It is the most common cause of hospitalization and acute illness in children under one years old,¹ with over 100,000 hospital admissions annually in the United States.² Total inpatient healthcare costs exceed \$1.7 billion dollars annually.³ Epidemiologic data suggests that respiratory syncytial virus, or RSV, is responsible for approximately 65% of hospitalizations due to bronchiolitis.⁴ Other viral culprits of bronchiolitis include, but are not limited to, rhinovirus, human bocavirus, human metapneumovirus, adenovirus, coronavirus, and influenza.⁵ Bronchiolitis is generally seasonal, with the majority of cases occurring in the winter months. However, patients who are immunosuppressed may be vulnerable to RSV infection throughout the year. RSV infection does not award lifelong immunity, and reinfection throughout life is common. Because this disease process is so prevalent in pediatrics, and is a common cause for significant respiratory distress in infants, primary care providers and emergency department clinicians alike need to be well versed in treatment modalities for acute bronchiolitis.

Bronchiolitis first begins in the upper respiratory tract and then spreads distally to the lower respiratory tract within a few days. Subsequent inflammation in the bronchioles follows due to both the infiltration of mononuclear cells and edema of the submucosa. Consequently, necrotic epithelial tissue and fibrin occlude the airway to varying degrees. As the cellular debris is cleared from the airway via coughing or immune response mechanisms, the patient's clinical picture can rapidly change and result in an inaccurate diagnosis or an underappreciated severity of the illness. Air trapping distal to the site of obstruction can create atelectasis and a mismatch of ventilation and perfusion that may lead to hypoxemia, particularly in infants who have poorly

developed collateral ventilation pathways. Receiving high flow supplemental oxygen can exacerbate atelectasis due to its proclivity to rapid absorption compared to room air. Smooth-muscle constriction plays very little role in the pathogenesis of bronchiolitis, which explains the limited benefit of bronchodilator therapy in treating this disease.⁶

Initially, signs and symptoms of bronchiolitis are similar to the common cold. These include cough, fever, rhinorrhea, nasal congestion, fatigue, and irritability. Later on in its course, the cough worsens and wheezing and rales can develop. More serious signs and symptoms include poor feeding, dehydration, tachypnea, increased work of breathing, and even cyanosis.

Importantly, bronchiolitis is a clinical diagnosis. The American Academy of Pediatrics has stated that evidence-based reviews have not shown support for the role of any diagnostic testing in managing routine bronchiolitis.² With that being said, chest radiographs may show hyperinflation of the lungs indicative of air trapping, as well as atelectasis¹. Rapid viral antigen testing is another tool in the diagnostic arsenal, but because most viral infections have similar courses in bronchiolitis, viral testing adds little to its management.

The treatment of bronchiolitis has been heavily studied and continues to be an area of active research. The American Academy of Pediatrics (AAP) recently revised its 2006 clinical practice guideline with respect to the management of acute bronchiolitis in 2014.² The AAP advocates against the use of bronchodilators with and without epinephrine to infants and children with a diagnosis of bronchiolitis. The AAP also recommends against systemic corticosteroid use, chest physiotherapy, and antibacterial medications unless secondary bacterial infection is suspected. Interestingly, the AAP suggests the use of nebulized hypertonic saline to infants and children hospitalized with bronchiolitis, but not to patients in the emergency department setting.² Research has shown that nebulized hypertonic saline can increase mucociliary clearance by

decreasing the viscosity of mucus secretions and airway edema as the hypertonicity of the solution generates water absorption from the bronchiole submucosa.⁶ Similarly, inhaled hypertonic saline has long been an accepted treatment in cystic fibrosis patients by acutely improving mucociliary clearance. Although the pathophysiology of cystic fibrosis and bronchiolitis are much different, the disease processes are similar in that both involve mucus plugging and slowed mucociliary clearance.

The efficacy regarding the use of nebulized hypertonic to decrease hospital admission rates from an emergency department setting is conflicting and remains unclear.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not nebulized hypertonic saline solution reduces hospital admission rates when compared to nebulized normal saline solution in children less than or equal to 24 months of age diagnosed with acute bronchiolitis in the emergency department setting.

METHODS

The studies that were selected during the construction of this EBM review were three randomized, double-blind, placebo controlled trials.^{7, 8, 9} The population studied in the trials included children with the diagnosis of acute bronchiolitis in the emergency department from ages 6 weeks to 24 months of age. The interventions in each study involved administration of nebulized hypertonic saline solution; Wu et al and Florin et al used 3% saline whereas Jacobs et al used 7% saline. For reference, normal saline solution is 0.9% sodium chloride. The outcome measured that is of particular interest to this EBM review was hospital admission rate.

Using PubMed and Cochrane databases, I researched the three selected studies.

Keywords used in the literature search were “nebulized hypertonic saline”, “bronchiolitis”, and “admission rate”. All articles were published in English in peer-reviewed journals and were selected based on significance and application, as well as the condition that outcomes measured were patient oriented outcomes (POEMS). Inclusion and exclusion criteria were similar across all three articles. Inclusion criteria involved children less than 24 months of age with a primary diagnosis of acute bronchiolitis in the emergency department. Exclusion criteria were patients over 24 months of age, patients with pre-existing heart, lung, or kidney disease, patients born at less than 34 weeks gestational age, patients with a history of asthma, and those in which informed consent could not be obtained. **Table 1** demonstrates the demographics of the studies included in this EBM review. The statistics used were relative risk reduction (RRR), absolute risk reduction (ARR), number needed to treat (NNT), and p-values.

Table 1: Demographics & Characteristics of included studies

Study	Type	#Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Wu ⁷ (2014)	Double blind RCT	408	≤ 24 months	Pts ≤ 24 months with a primary diagnosis of bronchiolitis during bronchiolitis season (November-April).	Patients with a history of wheezing or bronchodilator use, gestational age ≤34 weeks, or those with congenital heart disease, lung disease, or tracheostomy.	24	4mL of 3% nebulized hypertonic saline
Jacobs ⁸ (2014)	Double blind RCT	101	6 weeks to ≤ 18 months	Patients age 6 weeks to ≤18 months presenting to the ED from October-March from 2010-2012 with a diagnosis of bronchiolitis.	Patients with a history of wheezing, bronchodilator use within 2 hours of presentation, gestational age ≤34 weeks, history of congenital heart disease, chronic pulmonary disease,	0	0.5mL 2.25% racemic epinephrine mixed with 3mL of 7% hypertonic saline

					chronic renal disease, O ₂ sat of ≤85% at time of recruitment, severe disease requiring ICU admission, or inability to obtain informed consent.		
Florin ⁹ (2014)	Double blind RCT	62	2 months to ≤ 24 months	Patients aged 2 months to ≤24 months presenting to the ED with a first episode of acute bronchiolitis, defined as their first episode of wheezing with signs and symptoms of respiratory distress and upper respiratory infection.	Infants with history of wheezing or asthma, history of bronchodilator therapy, chronic lung or heart disease, critical illness, and inability to receive nebulized medication. Infants with non-English-speaking guardians were excluded because of inability to provide fully informed consent within the study time constraints.	0	4mL of 3% nebulized hypertonic saline

OUTCOMES MEASURED

Outcomes measured were those of patient-oriented evidence that matters (POEMS). Each article measured the hospital admission rate when nebulized hypertonic saline solution was administered, compared to that of administered nebulized normal saline solution in the emergency department setting. Admission rate was calculated as the number of patients requiring inpatient hospitalization divided by the total number of patients randomized.

RESULTS

Three randomized, controlled trials were analyzed in this review. Each study compared nebulized hypertonic saline solution to nebulized normal saline solution in children less than or equal to 24 months of age with acute bronchiolitis in emergency department settings. Children with a history of wheezing or asthma, chronic heart or lung disease, severe disease, gestational

age less than or equal to 34 weeks, bronchodilator use prior to arrival, or those with inability to obtain informed consent were excluded from the studies.^{7, 8, 9}

The study by Wu et al⁷ recruited 408 patients from the emergency department from March 1st, 2008 through April 30th, 2011. These patients were recruited from two freestanding urban children's hospitals in California. Seven patients from each study group left or were transferred before receiving treatments, seven patients were withdrawn due to parent request, and three patients were withdrawn due to a change in diagnosis. Patients received 2.5mg of nebulized albuterol sulfate followed by 4mL of either nebulized hypertonic or normal saline. In the group that received nebulized normal saline, 84 patients out of 192 patients (43.8%) required admission compared to the 61 patients out of 192 (31.8%) in the group that received the nebulized hypertonic saline solution. The difference in admission rate between the two groups remained statistically significant ($p = 0.01$) after adjusting for sociodemographic clinical predictors such as male sex, patient weight, baseline respiratory rate, and baseline oxygen saturation. The absolute risk reduction (ARR) was 12%, and thus patients with bronchiolitis had a 12% absolute lower risk of being admitted to inpatient care with nebulized hypertonic saline compared to control. The number needed to treat (NNT) to prevent 1 hospitalization was 8 patients.

The study by Jacobs et al⁸ recruited 101 patients from an emergency room in an urban tertiary care center between October 2010 and March 2013. This study was different from the other two studies in the fact that the intervention studied had a much higher tonicity (7%) than the 3% saline solution the other two studies chose to analyze. In this study, 22 out of 52 patients (42%) in the intervention group were admitted to inpatient care compared to 24 out of 49 patients (49%) in the normal saline control group. The number needed to treat to prevent 1 hospitalization was 15 patients. The statistical significance (at the 0.05 significance level) was reported as an

odds ratio with a 95% confidence interval as a proportion of the p-value. This study found that the difference in the proportion of patients admitted in each group was not statistically significant as the confidence interval contains 1.0.

The third study by Florin et al⁹ recruited 62 patients from a tertiary care emergency department from November 1st, 2010 to April 30th, 2011. This randomized controlled trial administered either nebulized hypertonic saline or normal saline within 90 minutes after a trial of nebulized albuterol and nasal suctioning. There were 22 out of 31 patients (71%) admitted in the hypertonic saline group compared to 20 of 31 patients (65%) admitted in the normal saline group. Interestingly, the number needed to treat was -16, and thus for every 16 patients treated with nebulized hypertonic saline, there is 1 less patient prevent from becoming hospitalized. However, the difference in admission rate was not statistically significant with a p-value of 0.86.

Table 2 demonstrates the statistics reported in each of the studies included in this EBM review.

Table 2: Efficacy of nebulized hypertonic saline in reducing hospital admission rate

Study	CER	EER	RRR	ARR	NNT	P value (95% CI)
Wu ⁷	0.56	0.68	0.21	0.12	8	0.01
Jacobs ⁸	0.51	0.58	0.14	0.07	15	OR= 0.76 (0.35-1.7)
Florin ⁹	0.35	0.29	-0.17	-0.06	-16	0.86

DISCUSSION

The study by Wu et al claims to be the largest study evaluating the efficacy of hypertonic saline solution in the treatment of acute bronchiolitis with 384 patients, and it found the

intervention to significantly reduce the hospital admission rate when given in the emergency department. The duration of action of the hypertonic saline was rapid, and most of the patients only received one dose of the medication in this study. This individual study demonstrated convincing evidence that nebulized hypertonic saline solution could reduce hospital admission rate when administered in the emergency department. As discussed previously, bronchiolitis is a major contributor to hospitalization in children, which causes significant morbidity in the pediatric population. With that being said, this study is persuasive given the sizable study population recruited for this specific analysis.

One of the major limitations to the Wu et al study was the fact that the majority of patients recruited were Hispanic, and thus the generalizability of the study is quite limited. As mentioned earlier, those with congenital heart and lung defects were excluded from the study (in addition to all of the studies this EBM review analyzed) and, consequently, the results cannot be applied to the pediatric population with these defects.

Jacobs et al chose to look at 7% nebulized hypertonic saline solution compared to nebulized normal saline in 101 patients. Both intervention and control were mixed with 0.5mL 2.25% racemic epinephrine and driven by 6L per minute oxygen flow. Infants with acute bronchiolitis presenting to the emergency department had a 7% lower risk of being hospitalized compared to control, however it was found to be statistically insignificant and drawing any conclusions from the data reported would be inappropriate. It is important to note that this study had less than 25% of the sample size Wu et al had studied.

There were several limitations to this study. First, admission rate, although an outcome the study chose to compare, was actually a secondary outcome and not the primary purpose of the study. Therefore, this randomized controlled trial was not designed nor intended for the study

of hospital admission rate. Moreover, the study population was infants with moderate bronchiolitis, and so the potential benefit of 7% hypertonic saline in severe bronchiolitis cannot be excluded.

The study by Florin et al was interesting in the fact that it analyzed the effects of hypertonic saline solution in children with persistent respiratory distress one hour after subsequent bronchodilator therapy and nasal suctioning. With respect to admission rate, the study found nebulized hypertonic saline solution actually worsened patient outcomes in regards to admission rate compared to nebulized normal saline. Florin et al explained several potential mechanisms for their findings. One rationalization is that hypertonic saline, as well as albuterol, can transiently increase bronchial secretions and thus can induce cough. Because patients who present to the emergency department already have intensified symptoms and disease presentation, the hypertonic saline may have had an additive effect on the nebulized albuterol, and caused increased symptoms and temporary respiratory distress resulting in admission. However, the increase in admission rate was not statistically significant when compared to control.

This study presented several limitations, one of which being the timing of drug administration. The delivery of the albuterol and 3% hypertonic saline was intended to be such that the patient was to be assessed as the effects of hypertonic saline peaked, but well after the peak of albuterol. The possibility of residual effects from albuterol exists, interfering with the effects of the hypertonic saline and thus confounding results. Secondly, the number of patients recruited in this study was only 62, by far the smallest study population of the three trials analyzed. Consequently, even though the intervention group had a 71% admission rate compared to the 65% in the control group, the difference was only a matter of 2 patients. The small sample

size, relative to how prevalent bronchiolitis is in this age group, may be too limited to draw proper conclusions.

One of the largest limitations to each of the studies was the use of bronchodilator therapy. The use of hypertonic saline is an established diagnostic test in asthmatics as a way to separate those with the disease from those without.¹⁰ Hypertonic saline has dose dependent effects, and can induce bronchospasm in asthmatics. The concentrations used for this diagnostic test range from 4.5%-7%.¹¹ However, as mentioned previously, bronchiole hyperresponsiveness is not a pathophysiologic feature of bronchiolitis as it is in asthma, and thus hypertonic saline theoretically should not induce such bronchospasm in patients with bronchiolitis without concomitant asthma. There was a retrospective cohort study¹² that looked at the adverse effect profile of nebulized 3% hypertonic saline in 68 patients with acute bronchiolitis. A total of 377 doses were administered without a bronchodilator, with a resultant 1% adverse event rate. The study notes that most adverse events were mild (being described as coughing), but one adverse event was classified as bronchospasm. Due to these findings, subsequent studies evaluating hypertonic saline's efficacy in the setting of acute bronchiolitis utilize a bronchodilator with the intervention to potentially mitigate the potential risk for bronchospasm. For that reason, the studies were all limited because the bronchodilator therapy may have had an interacted with the intervention such that the benefit of hypertonic saline was masked or interfered with. Additionally, there is no way to discern the children with hyperreponsive bronchioles who will eventually be diagnosed with asthma from those without. Hence, there is no current method to identify how many of each future asthmatic was in each study group, which could affect admission rate since the pathophysiology and treatment of asthma exacerbation is different than

that of bronchiolitis. Lastly, the 7% nebulized hypertonic saline that Jacobs et al used could have induced bronchospasm in that subset of patients with reactive airways.

Because emergency rooms are obligated by federal law to provide care to all patients irrespective of their ability to pay, insurance coverage was not an issue in any of the studies. Additionally, nebulized hypertonic saline is inexpensive and widely available in the United States, making it easily obtainable for patients if need be. Therefore, insurance and access to the study drug were non-issues and did not affect the results of the studies.

CONCLUSION

The trials analyzed in this EBM review showed conflicting evidence regarding nebulized hypertonic saline solution's capacity to reduce hospital admission in patients with bronchiolitis in the emergency department. The study by Wu et al demonstrated the most convincing data that such an intervention reduces admission rate, as well as was the largest study to date analyzing this topic. Jacobs et al suggested nebulized hypertonic saline reduces admission rate with a smaller study population, but the data was not statistically significant. Lastly, Florin et al found that nebulized hypertonic saline actually produces worse outcomes when it regards hospitalization rate, but again was not statistically significant.

Future study is warranted to definitively evaluate the efficacy of nebulized hypertonic saline at reducing admission in the setting of acute bronchiolitis. Additionally, populations for future studies should ideally be large and diversified to eliminate the argument that small study population and narrow racial representation may have led to inaccurate results. Because the American Academy of Pediatrics recommends against the use of bronchodilator therapy in the management of acute bronchiolitis without concomitant respiratory disease, future study may benefit from the use of nebulized hypertonic saline without such bronchodilator therapy.

REFERENCES

1. Bramson RT, Griscom NT, Cleveland RH. Interpretation of chest radiographs in infants with cough and fever. *Radiology*. 2005;236(1):22-29. <http://dx.doi.org/10.1148/radiol.2361041278>. doi: 10.1148/radiol.2361041278
2. Ralston SL, Lieberthal AS, Meissner HC. Clinical practice guideline: The diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134(5):e1474-e1502.
3. Hasegawa K, Tsugawa Y, Brown DFM, Mansbach JM, Camargo CA. Trends in bronchiolitis hospitalizations in the united states, 2000–2009. *Pediatrics*. 2013;132(1).
4. Weber, M.W., Mulholland, E.K., and Greenwood, B.M. Respiratory syncytial virus infection in tropical and developing countries. *Tropical Medicine & International Health*, 1998; **3(4)**: 268-80.
5. Stempel HE, Martin ET, Kuypers J, Englund JA, Zerr DM. Multiple viral respiratory pathogens in children with bronchiolitis. *Acta paediatrica (Oslo, Norway : 1992)*. 2009;98(1):123-126. doi:10.1111/j.1651-2227.2008.01023.x.
6. Mandelberg A, Tal G, Witzling M, Someck E. Nebulized 3% hypertonic saline solution treatment in hospitalized infants with viral bronchiolitis. *Chest*. 2003;123(2):481
7. Wu S, Baker C, Lang ME, et al. Nebulized hypertonic saline for bronchiolitis: A randomized clinical trial. *JAMA Pediatr*. 2014;168(7):657-663. doi: 10.1001/jamapediatrics.2014.301
8. Jacobs JD, Foster M, Wan J, Pershad J. 7% hypertonic saline in acute bronchiolitis: A randomized controlled trial. *Pediatrics*. 2014;133(1):e8-13. doi: 10.1542/peds.2013-1646
9. Florin TA, Shaw KN, Kittick M, Yakscoe S, Zorc JJ. Nebulized hypertonic saline for bronchiolitis in the emergency department: A randomized clinical trial. *JAMA Pediatr*. 2014;168(7):664-670. doi: 10.1001/jamapediatrics.2013.5306
10. Mai, X.-M., Nilsson, L., Kjellman, N.-I. M. and Björkstén, B. (2002), Hypertonic saline challenge tests in the diagnosis of bronchial hyperresponsiveness and asthma in children. *Pediatric Allergy and Immunology*, 13: 361–367. doi: 10.1034/j.1399-3038.2002.01011.x
11. Büchele G, Rzehak P, Weinmayr G, et al. Assessing bronchial responsiveness to hypertonic saline using the stepwise protocol of phase two of the International Study of Asthma and Allergies in Childhood (ISAACII). *PediatrPulmonol*. 2007;42(2):131–140
12. Ralston S, Hill V, Martinez M. Nebulized hypertonic saline without adjunctive bronchodilators for children with bronchiolitis. *Pediatrics*. 2010;126(3):e520.