Does Normal Saline Have Clinical Effects in Infants with Bronchiolitis?

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SUMMARY

The objective of this systematic review and meta-analysis was to measure the short-term association of nebulized normal saline with physiologic measures of respiratory status in children having bronchiolitis by comparing nebulized normal saline with the use of other placebos. Randomized clinical trials comparing children 2 years or younger with bronchiolitis who were treated with nebulized normal saline were included. Studies enrolling a treatment group receiving an alternative placebo were included for comparison of normal saline with other placebos. Pooled estimates of the association with respiratory scores, respiratory rates, and oxygen saturation within 60 minutes of treatment were generated for nebulized NS *vs* another placebo and for change before and after receiving nebulized normal saline. A total of 29 studies including 1583 patients were included. Standardized mean differences in respiratory scores for nebulized normal saline *vs* other placebo (3 studies) favored nebulized NS by –0.9 points (95% CI, –1.2 to –0.6 points) at 60 minutes after treatment (P<0.001). The standardized mean difference in respiratory score (25 studies) after nebulized NS was –0.7 (95% CI, –0.7 to –0.6; I^2 = 62%). The weighted mean difference in respiratory scores using a consistent scale (13 studies) after nebulized NS was –1.6 points (95% CI, –1.9 to –1.3 points; I^2 = 72%). The weighted mean difference in respiratory rate (17 studies) after nebulized NS was –5.5 breaths per minute (95%CI, –6.3 to –4.6 breaths per minute; I^2 = 24%). The weighted mean difference in oxygen saturation (23 studies) after nebulized NS was –0.4% (95% CI, –0.6%to –0.2%; I^2 = 79%). The authors concluded that nebulized normal saline may be an active treatment for acute viral bronchiolitis and recommended that further evaluation should occur to establish whether it is a true placebo.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: Bronchiolitis is one of the most common pediatric respiratory conditions, yet clinical experience and a vast body of research evidence suggests that 'nothing really works' as a treatment. In fact, the evidence for therapeutic options has been explored several times over the past decade in this journal itself, without satisfactory resolution. The United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines published in 2015, recommend against using hypertonic saline, nebulized adrenaline, salbutamol, montelukast, ipratropium bromide, antibiotics, systemic or inhaled corticosteroids, and combinations of systemic corticosteroids and nebulized adrenaline [1]. These conclusions were based on current evidence failing to demonstrate a lack of superiority of these treatments compared to placebo. It is instructive that almost all experiments on nebulized pharmacologic agents used 0.9% (normal) saline as the vehicle for delivering the medication. Not surprisingly, normal saline was chosen as the placebo in most comparative trials. Recently, House, *et al.* [2] undertook a systematic review and meta-analysis, re-exploring the evidence base to determine if normal saline has clinical effects and whether it can be truly considered a placebo.

Critical appraisal: ***Table* I** summarizes a critical appraisal of the systematic review using one of the checklists designed for this purpose [3]. Several additional points merit considerations.

Although this study [2] is not a systematic review comparing two interventions in the strict sense of the term, for practical purposes it devolves to a comparison of using nebulized normal saline *versus* not using it. Therefore, the authors chose to include studies having two types of comparisons. One comparison was nebulized saline *versus* some other placebo (compared against each other). The other comparison was before-*versus*-after effects of normal saline in trials wherein it was used (as placebo) in one of the arms. It can be argued that the authors should have additionally searched for single-arm studies of nebulized normal saline alone, analyzing the before-*versus*-after effects. Such studies would likely have been conducted years before active pharmacologic interventions were examined.

Table I Critical Appraisal of the Systematic Review

Validity	
1. Is there a clearly focused clinical question?	Although the authors did not explicitly frame a clinical question for the systematic review, the PICOT components can be summarized as: P: Infants with a clinical diagnosis of acute viral bronchiolitis. I: Nebulized normal saline C: No normal saline or any placebo other than normal saline O: Respiratory distress score, respiratory rate, oxygen saturation T: Within 60 minutes.
2. What are the criteria for selection of studies?	The authors included clinical trials that matched the above PICOT criteria.
3. Is the literature search method specified?	Two large databases *viz* MEDLINE and Scopus, were searched (from inception to March 2019) for relevant literature. The search terms for each database were reported. Additionally, reference lists of relevant publications were hand-searched. There was no language restriction. However, the authors did not search Conference abstracts/proceedings and publicly available student theses. Likewise, registries of clinical trials were not examined.
4. Have the identified studies been evaluated for methodological quality?	The authors used the revised Cochrane Risk of Bias tool for methodological assessment, and reported the results.
5. Is it appropriate to combine the results from different studies?	The results from the included studies can be combined.
Results	
1. Were the results consistent from one study to another?	There was significant heterogeneity for some outcomes. The authors explored these through pre-specified subgroup analyses, as well as comparison of results with the fixed *versus* random effects models of meta-analysis.
2. What were the overall results of the review?	Nebulized normal saline *versus* other placebo • Respiratory score SMD: -0.9 (95% CI -1.2, -0.6); 3 trials. • Respiratory rate: No statistically significant difference* • Oxygen saturation: No statistically significant difference* Nebulized normal saline *versus* no saline (before/after model) • Respiratory score SMD: -0.6 (95% CI -0.7, -0.5); 25 studies. • Respiratory rate MD: -5.1 (95% CI -6.4, -3.9), 17 studies. • Oxygen saturation: MD -0.3 (95% CI -0.7, 0.1), 23 studies. Results of subgroup analyses of inpatient *versus* outpatient treatment were in line with the overall results. Likewise, results of 13 studies that used the same respiratory scoring system were comparable to the overall results. Step-wise sensitivity analyses deleting outlier results, and those with high risk of bias, also yielded comparable results.
3. How precise were the results?	The pooled confidence intervals for the three outcomes are very narrow, suggesting high degree of precision.
Applicability	
1. Is the local population similar to those included in the original studies?	Yes.
2. Is the intervention feasible in my setting?	This systematic review was not designed to test the clinical efficacy of nebulized normal saline *per se*, but to explore whether it can be truly considered a placebo. The intervention should not be tried in any setting for the reasons highlighted in the text.
3. Have all the clinically relevant results been taken into consideration?	Only a limited number of outcome measures were considered in this analysis. Further, no outcomes were examined beyond 60 minutes.
4. Do the benefits outweigh the potential harm?	*See additional comments in the text.*

**The authors did not show data for these outcomes, but mentioned the conclusion; MD=Mean difference; SMD=Standardized mean difference.*

Although before-*versus*-after comparison of outcomes within the placebo arm of trials is a smart way to examine potential effects of normal saline, this could be confounded by the effects of supportive management particularly oxygen and/or fluids. In this regard, it is notable that 11 of 14 trials among out-patients used oxygen to drive nebulization. Only two [4,5] used room air; and one [6] did not clearly report the use of oxygen (or otherwise). Only one trial among in-patients [7] did not mention the use of oxygen. Further, before-*versus*-after analysis of normal saline effects cannot tease out the effect of time on the recovery process in bronchiolitis. Although this is theoretically true of all studies using multiple doses of (any) intervention, it is especially relevant in bronchiolitis.

The authors [2] separately analyzed studies wherein normal saline could be compared against another placebo. This is the only type of study design wherein a potential effect of normal saline can be determined without confounding by factors mentioned above. There were three such studies. Two of these [4,5] by the same group of investigators had an arm wherein infants received oral rehydration solution (ORS) while the third study [8] had an arm wherein infants received "mist in a tent". However, the details of mist administration were not specified. Combining the trials with ORS, the authors [2] reported the weighted mean difference for respiratory distress score as -1.6 (95% CI -0.8, -0.03), suggesting an overall benefit with saline. However, this seems implausible as the pooled effect lies outside the confidence interval. Further, even if there was a statistically significant reduction in the severity score by 1.6, its clinical significance is questionable given that the scoring system had a range from 0 to 27 [4]. This view is supported by the fact that normal saline did not have any impact on respiratory rate or oxygen saturation. In fact, the authors of one of the trials [4] themselves commented that there was comparable improvement in the three trial arms (nebulized salbutamol, nebulized normal saline, ORS) suggesting that the effect was related to change in the infants' state and/or disease process with time.

The authors [2] chose to include only three short-tern outcomes in the systematic review. Some of the other relevant outcomes are heart rate, need for escalation of therapy/additional doses, failure to improve within 60 minutes, change in sensorium, requirement of intensive care, and ventilation support. Even mortality within the first few hours could be included as an outcome. Among these, heart rate would have been especially useful because decline in heart rate within the first 60 minutes would likely reflect the benefits of oxygen and/or supportive care, rather than saline. Unfortunately, this was not explored.

The forest plot for oxygen saturation in the systematic review [2] shows a marginal but statistically significant decline with nebulized normal saline, but this was erroneously interpreted as "improvement with normal saline."

Last, but not the least, 14 of the 25 studies in the meta-analysis [2] showed a statistically significant improvement in respiratory score with normal saline. In 10 of these [4-6, 9-15], the effect of nebulized normal saline was comparable to the active intervention. These encompassed a wide variety of nebulized medications *viz*, salbutamol (in 7 trials), epinephrine (in 4 trials), hypertonic saline (in 2 trials), ipratropium (in 1 trial), terbutaline (in 1 trial), furosemide (in 1 trial), salbutamol + ipratropium (in 1 trial), and salbutamol + hypertonic saline (in 1 trial). If normal saline is interpreted as having statistically significant effects (as reported in the systematic review), then the inescapable conclusion is that all these interventions also have significant effects. Further, in trials showing superiority of various interventions over normal saline (salbutamol in 7 trials, epinephrine in 2 trials, hypertonic saline in 1 trial, ipratropium in 1 trial, epinephrine + dexamethasone in 1 trial) the effects can be attributed to the synergistic combination of the active pharmacologic agent with normal saline (since normal saline was the vehicle for nebulization in all the trials). Further, such an interpretation would necessitate extrapolating this conclusion to other conditions where nebulized treatments work, most notably bronchial asthma! The time, effort, money and risk to patients if this line of thought is pursued through new trials to prove (or disprove) this is unimaginable.

Conclusion: This systematic review [2] raised the possibility that nebulized normal saline may have some clinical effects in infants with bronchiolitis, hence may not truly be a placebo. However, the limited evidence comparing saline against a true placebo, methodological issues, and interpretation of data, make it difficult to concur with this view. In any case, it seems unwise to explore the issue further through new clinical trials.

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Pediatric Pulmonologist's Viewpoint

Bronchiolitis is a common cause of hospitalization among children less than two years of age. It is a lower airway disease affecting infants and children and caused by viral infections. Most common virus associated with bronchiolitis is RSV, attributed in >80% of children. The pathophysiologic lesion in bronchiolitis is epithelial necrosis and dense plug formation in the bronchiolar lumen leading to air trapping and mechanical interference with ventilation.

Bronchiolitis is a self-limited illness and often resolves without complications in healthy infants. For children with non-severe bronchiolitis, no pharmacologic interventions are recommended as there is no evidence of benefit. It may increase the cost of care and may have adverse effects. Children with severe bronchiolitis, require admission and supportive care. Supportive care includes maintenance of adequate hydration, provision of oxygen and respiratory support as required and disease progression monitoring. Guidelines recommend discouragement of routine use of inhaled bronchodilators (albuterol or epinephrine), nebulized hypertonic saline and systemic/inhaled glucocorticoids. However, a one-time trial of inhaled bronchodilators may be done for children with severe bronchiolitis.

In the index paper (systematic review and meta-analysis), placebo status of nebulized normal saline (NS) was evaluated in acute bronchiolitis. The main outcome measure was the association of nebulized NS with respiratory score, respiratory rate and oxygen saturation within 60 minutes of treatment and for changes before and after receiving nebulized NS. The analysis has been done meticulously as is evident on its critical appraisal; however, the one major limitation is outcome analyzed within sixty minutes of therapy. This short-term improvement may be attributed to the variable, dynamic course of bronchiolitis as well as to the other treatment provided concurrently including oxygen, fluid, and antipyretics.

Until and unless there are evidence of association of nebulized normal saline with parameters *e.g.,* days of hospitalization, days of oxygen therapy, respiratory score, respiratory rate and oxygen saturation at the end of 48 hours or over a longer period, in comparison to standard treatment and other placebos, the results of the study cannot be generalized.

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