When should nebulized hypertonic saline solution be used in the treatment of bronchiolitis?

Jeffrey Hom MD MPH[1], Ricardo M Fernandes MD[2]

Bronchiolitis is a common lower respiratory infection that leads to frequent hospitalization at a rate of 31.2 per 1000 infants per year (1). Salbutamol, racemic adrenaline, corticosteroids and nebulized normal saline (NS) are commonly used therapies that all appear to have questionable efficacy in specific settings (2). The present review examines the effectiveness of nebulized 3% hypertonic saline solution (HS) in improving clinical scores, reducing the hospitalization rate and decreasing the length of stay (LOS), and reports adverse events attributed to HS.

PART A: EVIDENCE-BASED ANSWER AND SUMMARY

MEDLINE, EMBASE and the Cochrane Library were searched for randomized controlled trials that treated children with nebulized HS for bronchiolitis. One Cochrane meta-analysis published in 2008 (3) concluded that HS improved clinical scores on the first and second but not on the third day of treatment, did not decrease the hospitalization rate in the single small outpatient study, but did reduce LOS. The present review includes the four studies (4-7) from the meta-analysis and three subsequent studies (8-10).

The challenge of the review is the heterogeneity of these studies. The mean ages of the children in the studies ranged from 2.6 months (6) to 12.5 months (4). Children were enrolled from outpatient community clinics in Israel (4), paediatric emergency departments (EDs) in Canada (9) and Turkey (10), and inpatient wards in Israel (5,6), China (8), and both the United Arab Emirates and Canada (7). None of the studies enrolled children who required intensive care unit admission. Five studies (4-6,8,10) used the Wang clinical scoring system. The Respiratory Distress Assessment Instrument (7) and the Respiratory Assessment Change Score (9) were used by one study each.

All studies randomly assigned children to nebulized treatment groups of either 0.9% NS or 3% HS (4-10). In six studies (4-6,8-10), a protocol-specified bronchodilator was mixed and nebulized along with a saline solution, including terbutaline (4), salbutamol (8) or adrenaline (5,6,9), at variable dosing frequencies and durations. Two of these six studies (5,6) permitted the treating clinicians to provide 'add-on' nebulization treatments at their own discretion. The ED study from Turkey (10) had four treatment arms combining salbutamol or adrenaline with 0.9% NS or 3% HS, with a fifth arm receiving only 0.9% NS. In the seventh study (7), clinicians added a bronchodilator to the NS or HS at their discretion, with 37% of the treatments including salbutamol and 23% including adrenaline.

Results of clinical scores were inconsistent. The outpatient study and three inpatient studies (4-6,8) demonstrated a statistically significant greater improvement in the HS than in the NS group. These scores improved as the number of HS treatments increased. The remaining inpatient study (7) calculated a clinical score during enrollment, not after saline treatments. Finally, the two studies from the ED (9,10) failed to show any differences in clinical scores between the treatment groups.

In the outpatient clinic (4), two children from the NS group (n=32) required hospitalization, compared with three children from the HS group (n=33). In the ED study from Turkey (10), one child from the NS and salbutamol group (n=36), and one child from the HS and adrenaline group (n=39) required hospitalization. The remaining three arms did not have any children requiring hospitalization. In the ED study from Canada (9), 13 children from the NS group (n=23) and eight children from the HS group (n=23) required hospitalization (risk ratio 0.61; 95% CI 0.22 to 1.19).

The LOS of hospitalized children was statistically significantly shorter in the HS group in all four studies (5-8). Typically, HS shortened the LOS by approximately one day (typically from approximately four to three days), with the largest decrease being 1.4 days (8). However, the mean LOS was also longest in the latter study (6.0 days in the HS group versus 7.4 days in the NS group) (8).

There is concern that HS could precipitate bronchospasm in children with reactive airway disease. No serious adverse events were attributed to HS in the included trials, but because very few children received HS without a bronchodilator, this fact is not totally reassuring.

In summary, HS was associated with improved clinical scores in four of seven studies with no obvious pattern. Hospitalization rates were not clearly impacted by therapy, but a trend toward a decreased rate was shown in one ED study (9). However, a shortened LOS was consistently observed in noncritical hospitalized patients.

PART B: CLINICAL COMMENTARY

Treatment of bronchiolitis is an ever-controversial topic in paediatrics. Frequently used interventions, including bronchodilators and steroids, have failed to show consistent and clinically relevant effects in meta-analyses of randomized trials. Current practice guidelines recommend only supportive measures, given the absence of clear evidence for any other approach. The debate is set to continue as recent exploratory results from the large Canadian Bronchiolitis Epinephrine Steroid Trial (CanBEST) (11) revisit old strategies by suggesting the benefit of combining steroids and adrenaline in reducing admission rates.

For clinicians on the front line during every bronchiolitis season, the uncertainties of research findings are as striking as the

[1]*Department of Pediatrics/Emergency Services, Department of Emergency Medicine, New York University School of Medicine, New York, New York, USA;* [2]*Child and Family Department, Hospital de Santa Maria and Clinical Pharmacology and Therapeutics, Institute of Molecular Medicine, Lisboa, Portugal*

Correspondence: Dr Ricardo M Fernandes, Child and Family Department, Hospital de Santa Maria and Clinical Pharmacology and Therapeutics, Institute of Molecular Medicine, Avenida Professor Egas Moniz, Lisboa, Portugal 1649-035. Telephone 351-21-780-2123, fax 351-21-780-2120, e-mail ricardocunhafernandes@clix.pt

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burden of morbidity. Hospitalizations have been rising steadily in Canada and the United States (12,13), and there is persisting variation in management. A vaccine for respiratory syncytial virus has proven elusive and an effective treatment to reduce post-bronchiolitis wheezing is yet to be found. It is disappointing, to say the least, that the best we can offer our patients is monitoring, respiratory support and adequate hydration.

A new therapeutic approach is, therefore, welcome even if the intervention – ie, HS – sounds 'simple' and is not new to paediatric respiratory disease. Recent trials have highlighted its use in cystic fibrosis, with modest middle-term improvements in clinical and lung function outcomes (14). HS has the potential to hydrate airway surface liquid, thus improving impaired mucociliary clearance, and also to reduce airway wall edema through water absorption from the mucosa (15). All of these are predominant pathological features of acute bronchiolitis, and provide a rationale for the use of this treatment in this condition.

There are some promising results in the trials reviewed in part A of the present article. A mean reduction in LOS of approximately one day is clinically meaningful; no intervention tested against placebo for inpatient management has shown an effect size of this magnitude (16). In contrast, there was no improvement in clinical scores of outpatients in the ED setting, but one trial (9) did show a lower, albeit nonsignificant, admission rate, which may warrant further research. Adverse events were rare in trials that used saline alone or with a fixed bronchodilator, which confirms the favourable safety profile shown in infants with cystic fibrosis (17).

So, is HS the next big thing for bronchiolitis management? Decades of championing a number of failed interventions would suggest that caution should be advised. All trials included in the present review were small, often single centred and exploratory, and replication is needed to validate these findings. The absence of standardized, validated and patient-important outcomes has been a serious threat to bronchiolitis trial validity, and these trials are no exception. Clinically relevant differences for respiratory scores are unknown, and outpatient trials were underpowered to assess admission rates. Additionally, the approach to dosages, administration regimens and cointerventions is different in all trials. This limits analysis of a stand-alone effect of HS, as well as possible synergistic interactions, either using saline alone or with a specific bronchodilator. Larger trials assessing clinically relevant outcomes in both inpatient and outpatient settings are, therefore, needed.

Overall, results for nebulized HS are encouraging, and paediatricians should consider using it for inpatient management of bronchiolitis, because no other intervention has proven useful. For children in the ED, results are negative in studies completed to date. In this setting, bronchodilators such as adrenaline may provide minimal relief, and a combination of adrenaline and steroids shows promise, but needs to be studied further in future trials. Supportive measures remain the mainstay of bronchiolitis inpatient and outpatient management.

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