Nebulised hypertonic saline in moderate-to-severe bronchiolitis: a randomised clinical trial

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Received 5 March 2019
Revised 20 August 2019
Accepted 21 August 2019

To cite: Jaquet-Pilloud R, Verga M-E, Russo M, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2019-317160

ABSTRACT

Objectives To investigate whether nebulised hypertonic saline (HS) treatment would decrease length of hospital stay (LOS) among infants with moderate-to severe-bronchiolitis compared with standard supportive care (SC).

Methods We conducted an open, multicentre, randomised clinical trial from 1 April 2013 to 31 March 2016, in Swiss children's hospitals. Patients aged 6 weeks to 24 months with a primary diagnosis of moderate or severe bronchiolitis were included. Children with previous episodes of wheezing, cardiac disease, chronic respiratory disease, immunodeficiency, prematurity (gestational age <34 weeks), corticotherapy in the preceding 2 weeks or inhaled bronchodilators within 24 hours before presentation were excluded. Patients were randomised to receive standard SC with nebulisation of 4 mL of 3% sodium chloride every 6 hours versus SSC. Main outcomes and measures were LOS duration of oxygen therapy, transfer to intensive care unit (ICU), readmission within 7 days following discharge and adverse events.

Results 121 children were randomised. No statistically significant differences were found between treatment groups at baseline (age, Wang Score, atopic history, smoking exposure). Children in the HS group had a non-significant difference in length of stay −2.8 hours (−10; 16) compared with the SC group. There were no differences in oxygen therapy duration, transfer to ICU, readmission rate or adverse events. The intervention was discontinued at the parents' request in 16% of the cases.

Conclusion Our study does not support the use of HS nebulisation in children with moderate to severe bronchiolitis.

Trial registration number NCT01812525.

What is already known on this topic?

- Bronchiolitis is a leading cause of hospitalisation. The recommended treatment is supportive care. Some authors have advocated the use of nebulised hypertonic saline though studies that are more recent suggest that this is not a helpful intervention.

What this study adds?

- Inhaled nebulised hypertonic saline in patients with moderate or severe bronchiolitis did not decrease the length of hospital stay.

INTRODUCTION

Acute bronchiolitis is the the most common lower respiratory tract infection and the leading cause of hospitalisation in infancy.[1] The American Academy of Paediatrics defined bronchiolitis as a constellation of clinical symptoms and signs including viral upper respiratory symptoms followed by increased respiratory effort and wheezing in children less than 2 years of age.[2] The most frequent aetiology is the respiratory syncytial virus.[3–5] Approximately 3% of children with bronchiolitis are hospitalised and rates of hospitalisation have been increasing over time. Around 3% of these children require intensive care monitoring.[6 7] The only recommended treatment remains supportive care (SC).[2] Nebulised hypertonic saline (NHS) has been actively studied over the last 10 years with many randomised trials, but no consensus has been reached on its efficacy.[8] Some authors have suggested that hypertonic saline nebulisation may reduce airway oedema, decrease mucus plugging, improve mucociliary clearance and rehydrate the airway surface liquid in infants with bronchiolitis, though there is no experimental evidence to support this proposal.[9] In 2008 a Cochrane review showed that HS decreased length of hospital stay (LOS) by 1 day and reduced clinical severity scores in infants hospitalised with bronchiolitis.[10] Most recent trials and meta-analyses minimise NHS impact on LOS, and explain this difference by the substantial heterogeneity across trials in the definition of acute bronchiolitis, disease severity, use of bronchodilators with hypertonic saline (HS), outcome measures and LOS.[11–14] Furthermore in all trials but one, nebulised normal saline (NNS) was used as a placebo control solution.[15] However, it is to be considered as an active therapeutic agent rather than a placebo.[16–18] Only one trial compared nebulised hypertonic saline to standard SC and did not support its use.[15] In the light of these challenges, a pragmatic, open label, multicentre, randomised controlled trial was undertaken with children presenting with moderate-to-severe bronchiolitis. Patients were randomised to receive standard SC versus standard SC with NHS.

Design

This was a randomised multicentre clinical trial of nebulised 3% HS with standard SC compared with standard SC alone.

Setting

The study was conducted in two hospitals: one tertiary care centre (Lausanne Children's Hospital, Switzerland) and one secondary care centre in Sion, Switzerland, from 1 April 2013 to 31 March 2016.

Patients

Eligible patients included children aged from 6 weeks up to 24 months coming to the emergency department (ED) with a first episode of acute bronchiolitis, defined as symptoms of upper respiratory tract infection in addition to tachypnoea, wheezing and widespread crackles at auscultation. Further inclusion criteria were a Wang Score of 5–12 (moderate to severe) on arrival.[19]

Exclusion criteria were children with mild bronchiolitis (Wang Score <5), previous episodes of wheezing, cardiac or chronic respiratory disease, immunocompromised children, gestational age <34 weeks and children with critical illness requiring immediate admission to intensive care unit (ICU). Children who received RSV immunoglobulin therapy, corticotherapy in any form in the preceding 2 weeks or bronchodilators within 24 hours prior to presentation, were also excluded.

Participants were identified and recruited in the ED within the hour of arrival.

After informed parental consent was obtained, infants were randomly allocated on a 1:1 basis using a computer-generated randomisation program in blocks of 10 (Excel 2007, Macro in Visual Basic).

Interventions

Patients were randomised in two groups to receive either standard SC with no inhalation (SC group) or standard SC with inhalations of HS 3% (HS Group). The HS Group received 4 mL of NaCl 3% (*MucoClear 3%*) every 6 hours until discharge. *MucoClear 3%* is produced by PARI Gmbh (Germany). Pari LC sprint Nebulisers were used with an oxygen flow at 6 l/min. Two mask sizes were available for children aged <1 year or >1 year. Trained nurses administered HS.

Standard SC was similar in both groups. Standard therapy includes suctioning nasal secretions, water-electrolyte balance maintenance and oxygen supplementation when needed.

If any child showed signs of respiratory failure including either persistent major respiratory distress, signs of exhaustion with a partial pressure of carbon dioxide above >50 mm Hg on the capillary blood gas, a nebulisation of 4 mg of epinephrine was given.

Nebulised epinephrine could be administered up to three times within the hour. Despite a total of three nebulisations of epinephrine or in the absence of response, the patient was admitted to ICU.

Main outcome measure

Medical and family history, current and previous medications, immunisations, and parental smoking history were recorded. Observations including Wang Score, heart rate, body temperature, oxygen saturation in room air by pulse oxymetry, oxygen requirements and level of hydration were collected at admission. Nurses recorded respiratory rate, heart rate, oxygen saturation

Figure 1 CONSORT Flow Diagram

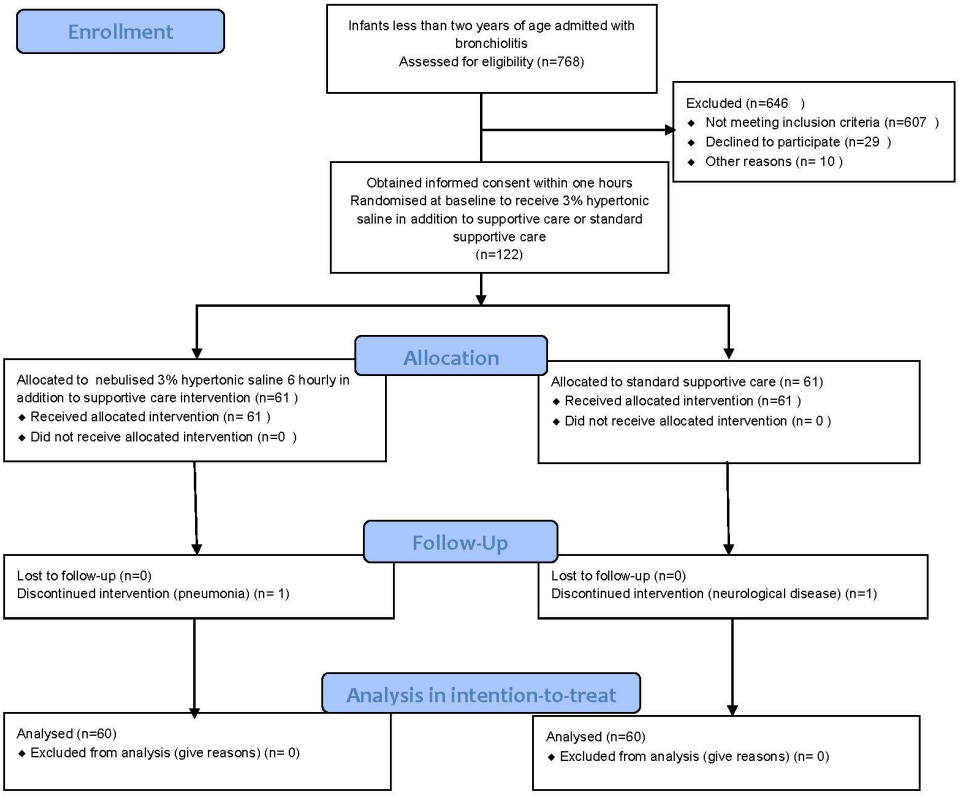

Figure 1 Consort flow diagram.

and oxygen requirement, every 6 hours for the control group and at the time of each inhalation therapy given and 30 min after for the intervention group. Physicians in charge of the ward assessed the Wang Score at 12 hours and 24 hours after the first nebulisation or at 12 hours and 24 hours after admission in the control group and once daily thereafter until discharge.

The primary outcome measure was LOS. It was defined as the time between entry in this study and the time at which the child reached criteria as measured by the physician in charge. Children were considered ready for discharge, that is, if he or she had not received supplemental oxygen for 10 hours with an oxygen saturation >90%, had a Wang Score <5 and was feeding adequately (taking 75% of their usual intake). The secondary outcome measures were: duration of oxygen therapy, need for racemic epinephrine nebulisation rescue therapy, transfer to ICU and adverse events such bronchospasm, excessive coughing, apnoea and cyanosis. Readmission rate in the next 7 days following discharge from hospital was studied.

Statistical analysis

Previous studies[13] showed that the mean (SD) LOS for infants admitted to hospital with bronchiolitis was 5 (±1.2) days. These studies also indicated that a reduction of 1 day in hospital was clinically significant.

To estimate our sample size we used an α risk of 5% and a power of 80%. A minimum sample of 120 patients (60 in each group) was calculated.

All statistical analyses followed the 'intention to treat' principle. Data were entered into a File Maker Pro V.11 (File maker Pro for Windows) and analysed with Stata V.13 (StataCorp LP, Texas, USA). Descriptive analyses were completed overall and for the control and study group separately. The χ^2 or Fischer's exact tests were used to examine association between categorical variables and groups. Quantitative variables between groups were compared using Student's t- test or Wilcoxon-Mann-Whitney test if there was an inequality of variance (Levene's test). To test the Wang Score evolution for both groups over time (baseline compared at 24.36 hours and 48 hours), a linear mixed-effects model with participants as a random effect on the square root of the Wang Score was run. The effects of time, group and their interaction were tested.

RESULTS

One hundred and twenty-two patients with moderate-to-severe bronchiolitis were enrolled between April 2013 and March 2016. One hundred and four patients were randomised in a tertiary centre Lausanne hospital and 18 patients in Sion hospital.

Sixty-one patients were allocated to the intervention group (HS) and 61 were allocated to the control group (standard care alone). One hundred and twenty patients completed the whole study. Two patients were excluded after randomisation, one for misdiagnosis (pneumonia) and the other for decompensation of an unknown neurological disease (figure 1).

There were no significant differences in baseline characteristics and clinical variables recorded: age, Wang Score on admission, gender, atopic dermatitis history, tobacco smoke exposure, dehydration between the intervention and control groups (table 1).

In the intention-to-treat analysis, no significant differences between both groups were found concerning the mean values and SD, median and range of LOS for the HS group (n=61) and the SCC group (n=59). The mean LOS in hours was 47 versus 50.4 (table 2). Ten participants did not receive treatment as expected. In an additional per protocol analysis in which these participants were excluded, the results were similar. There were also no significant differences found between the HS group and the SC group for mean duration of oxygen therapy, racemic epinephrine rescue therapy, transfer to paediatric ICU and readmission within 7 days after discharge. In addition, no statistically significant differences were observed in per protocol analyses for all secondary outcomes (data not shown).

Table 1 Patient demographic characteristics and illness status on admission for the nebulised hypertonic saline group and standard care group

Characteristics	Nebulised hypertonic saline n=61	Standard care n=59
Age, months		
Mean (95% CI)	7.7 (6.4 to 9.1)	7.5 (6.2 to 8.9)
Median (range)	6.3 (1.4 to 21.4)	6.1 (1.4 to 21.9)
Wang Score 9–12 N (%)	15 (24)	14 (23)
Wang Score 5–8 N (%)	46 (76)	45 (77)
Gender (female/male) N (%)	22 (36)	22 (37.3)
Atopic dermatitis history N (%)	8 (13)	4 (6.7)
Tobacco smoke exposure N (%)	20 (33)	19 (32)
Dehydratation N (%)	8 (13)	6 (10)

Wang Score decreases in both groups over time after inclusion. However, we observed statistically significant differences between groups at 24 hours and 36 hours with a greater improvement in the control group, but not at 48 hours (table 3).

We also did a sensitivity analysis to assess whether the baseline Wang Score affected length of stay. No statistically significant difference was observed in mean LOS in the subgroup with a Wang Score of >8 but the number of patients was low (15 and 14 patients) (table 4).

No statistically significant differences were observed in any of the secondary outcomes in the severe bronchiolitis (Wang Score >8) subgroup for the mean duration of oxygen, racemic epinephrine nebulisation rescue therapy, transfer to paediatric ICU and patients admitted within 7 days after discharge (table 4). No serious adverse events were observed (bronchospasm, excessive coughing, infection, apnoea and cyanosis) during the study. However, HS was discontinued in 10 patients at parents' request (sleep preservation (n=5), agitation with the inhalation facemask (n=5)). Five patients were admitted to hospital again within 7 days after discharge. Two patients in each group were readmitted for persisting symptoms of bronchiolitis (cough, nasal obstruction) and one patient had gastroenteritis.

DISCUSSION

This prospective multicentre randomised clinical trial comparing HS with standard SC versus standard SC alone, in children<2 years with moderate-to-severe bronchiolitis did not show any beneficial effects in LOS.

Our study confirmed the Hypertonic Saline in Acute Bronchiolitis Rct and Economic evaluation (SABRE) Study results, which also did not demonstrate any impact on mean LOS, readmission, adverse events of HS versus SC.[15] Although we used the same administration protocol of NHS, the same standard SC and specific criteria for time to discharge. In both studies, no beneficial effect of HS was observed for all outcomes.

Previous meta-analyses[10 20] showed that infants with mild-to-moderate acute viral bronchiolitis who were hospitalised and treated with HS versus NNS with or without bronchodilatators had a significantly shorter mean LOS in hospital. The results of

Table 2 Primary and secondary outcomes for the nebulised hypertonic saline group and the standard care group

	Nebulised hypertonic saline n=61	Standard care n=59	P values	Difference (95% CI)
Primary outcome				
Hospital length of stay (hours)				
Mean (95% CI)	47 (39 to 56)	50.4 (39 to 61)	0.33*	−2.8 (−11 to 16)
Secondary outcomes				
Duration oxygen therapy (hours)				
Mean (95% CI)	29.5 (22 to 36)	31.1 (22 to 39)	0.6*	−1.5 (−9.6 to 12)
Racemic epinephrine nebulisation rescue therapy N (%)	5 (8.2)	9 (15)	0.3†	
Transfers to paediatric intensive care unit N (%)	0 (0)	3 (5)	0.1†	
Patients admitted within 7 days of discharge N (%)	2 (3.2)	3 (5.1)	0.7†	

*T-test.
†Pearson test.

the meta-analysis of 2013 (11 trials, 1090 infants) showed that patients treated with NHS had a significantly shorter mean LOS compared with those treated with NNS (mean difference −1.15 days 95% CI −1.49 to 0.82 days). The review concluded that 'current evidence suggests HS may significantly reduce the mean LOS'.[20]

The 2015 systematic review and meta-analysis of Zhang included 15 studies and 1956 infants hospitalised with bronchiolitis.[21] This systemic review included two new European multicentre studies with relatively large sample sizes and did not find significant effects of NHS on LOS among inpatients. The mean difference was −0.45 days (95% CI −0.82 to −0.08) or −10.8 hours (95% CI −19.7 to −1.9) with a significant heterogeneity in results between studies. The results of this review showed that HS was less effective than in the previous review. The review concluded that 'HS is a safe and potentially effective treatment of infants with acute bronchiolitis'.

Brooks in 2016 in a re-analysis of meta-analyses between HS and NNS treatment groups found 18 studies included 2063 patients with a mean age of 4.2 months and mean LOS of 3.6 days.[11] Furthermore, Brooks included two European multicentre studies with a relatively large sample[22 23] published since 2015. Analysis of all studies showed a higher variability.

Brooks identified two main sources of heterogeneity, different criteria of discharge and imbalance in mean day of illness at randomisation. Two study populations used very different criteria for discharge, substantially longer expected LOS and the two studies were performed in the same centre in China. After exclusion of these studies, heterogeneity was acceptable and the mean difference between the HS versus the NS group was not statistically significant (−0.21 days; 95% CI −0.43 to +0.02).

Brooks found 6 of the 18 studies with a difference in the mean days of illness at presentationbetween NNS and HS treatment group patients admitted later in illness favouring the HS treatment group. After exclusion of these studies, heterogeneity decreased and the mean difference between the treatments was no longer statistically significant. The review concluded, 'The data did not support the use of HS to decrease LOS in infants hospitalised with bronchiolitis'.

Badgett published a living systematic review of nebulised HS for acute bronchiolitis among hospitalised infants.[24] This living systematic review shows a higher heterogeneity for LOS. All results of the studies published since 2012 were negative for LOS regardless of LOS (subgroup of LOS over or below 3 days). The reduction of LOS in favour of HS was confined to older trials with longer LOS.

However, our study has limitations. A critical point of our study is the absence of blinding. Our primary objective was the same as that of the SABRE study; make an open pragmatic study design reflecting our current practice consistent with recent clinical guidelines recommendations to determine if NHS might have a place in routine clinical practice. Other objective was removed potential effect of normal saline with/without bronchodilators used in the previous studies like nebulised placebo. Potential effect of NNS may be beneficial (humidify the airways) or deleterious (by disturbing and tiring infants).

The use of an active comparator such as NNS as a placebo in most trials, makes it difficult to discern the benefits of HS alone. NNS can be beneficial or detrimental in bronchiolitis. NNS may have some beneficial effects as it humidifies the airways but it may also disturb the clinical situation of infants with bronchiolitis. The apparent benefits of NHS may be secondary to the deleterious effect of NNS. The use of what constitutes a true placebo in trial design for nebulised therapies remains a dilemma if the study is blind.

In our study we had not controlled duration of illness before hospitalisation. Duration of illness can be a confounding factor as Brooks demonstrated.[11] Other limitations include the low statistical power for some secondary outcomes and for sensitivity analysis.

Treatment with HS was stopped in 10 (16%) patients at parents' request after a few days due to infant discomfort with inhalation by face mask. Nevertheless, the results are similar to those of the intention-to-treat analysis or per protocol analysis.

Table 3 Linear mixed-effects model analysis of the effects of time, group (standard care or nebulised hypertonic saline) and their interactions on the square root of Wang Score

	Coefficient (SE)	P values
Constant	2.69 (0.05)	<0.001
Time		
At inclusion	Ref	
At 24 hours	−0.73 (0.09)	<0.01
At 36 hours	−0.80 (0.09)	<0.01
At 48 hours	−0.68 (0.10)	<0.01
Group		
Standard care	Ref	
HS	−0.01 (0.08)	0.94
Time*group		
HS-24 hours	0.24 (0.12)	0.046
HS-36 hours	0.26 (0.12)	0.037
HS-48 Hours	0.02 (0.14)	0.877

HS, hypertonic saline.

Table 4 Outcomes for the nebulised hypertonic saline group and the standard care group in patients with severe bronchiolitis (Wang Score>8)

	Nebulised hypertonic saline n=15	Standard care n=14	P values
Primary outcome			
Hospital length of stay (hours)			
Mean (95% CI)	66 (43 to 88)	72 (48 to 95)	0.7*
Secondary outcomes			
Duration oxygen therapy (hours)			
Mean (SD) (95% CI)	46 (22 to 69)	54 (35 to 73)	0.6*
Racemic epinephrine nebulisation rescue therapy N (%)	3 (5)	6 (2.3)	0.4†
Transfers to paediatric intensive care unit N (%)	0 (0)	2 (7)	0.5†
Patients admitted within 7 days after discharge N (%)	0 (0)	0 (0)	NA

*Willcoxon-Mann-Whitney test.
†Fischer's exact test.

CONCLUSIONS

The results of this study confirm those reported by recent large studies or meta-analyses and support evidence against the use of HS in hospitalised infants with moderate or severe bronchiolitis. At present, the evidence seems to suggest that routine use of HS in bronchiolitis cannot be recommended. Minimal handling, oxygen administration, hydration and nutrition support remain the cornerstones of bronchiolitis treatment.

Acknowledgements The authors gratefully Dr Katia Iglesias for her precious statistical support and wise (School of Health Sciences (HEdS-FR), HES-SO University of Applied Sciences and Arts of Western Switzerland, Fribourg, Switzerland) and Dr Ermindo Di Paolo (Service of Pharmacy, Department of Laboratory, university hospital of Lausanne) for his precious support. The authors also thank the participating children and their parents.

Contributors RJ-P: conception, design and writing of the work. M-EV: conception, analysis interpretation of data and writing. MR: conception, design, revising the work critically. MG: conception, design, revising the work. J-YP: conception, design, analysis, interpretation of data writing. All authors read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval The study was approved by Swissmedic, Swiss Research Ethics Committee (No. 453/12).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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