

# **Saline in Acute Bronchiolitis RCT and Economic evaluation: hypertonic saline in acute bronchiolitis – randomised controlled trial and systematic review**

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## Scientific summary

### Saline in Acute Bronchiolitis RCT and Economic evaluation study

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# Scientific summary

## Background

Acute bronchiolitis is the most common cause of hospitalisation in infancy, with 1–3% of all infants admitted in their first year. The disease is caused by a number of common respiratory viruses, especially respiratory syncytial virus (RSV), and is associated with peaks in admissions in the winter months. Infants develop signs of an upper respiratory tract infection with rhinitis followed by signs of lower respiratory tract involvement due to lower airway obstruction. More laboured breathing, hyperinflation, cough and widespread crackles on auscultation are all sometimes accompanied by wheeze. Babies are most commonly admitted to hospital with this condition between 1 and 6 months of age.

Management consists of supportive care, supplemental oxygen, minimal handling and the provision of fluids. Oxygen therapy was introduced over 60 years ago and reduced mortality rates from 20% in the 1940s to less than 1%, although acute bronchiolitis still is a major cause of infant death. Paediatric inpatient services and paediatric intensive care units (ICUs) face enormous pressure from increasing admissions for acute bronchiolitis, as admission increased from 21,330 in 2004/5 to 33,472 in 2010/11. In the UK, the median duration of admission for all acute paediatric admissions is around 1.5 days, while the mean duration of hospitalisation for acute bronchiolitis is around 3.3 days. Treatments, including oral and inhaled steroids, antiviral agents and a variety of bronchodilators, have not impacted on the course of the acute illness or decreased the duration of hospitalisation.

It has been suggested by some published studies that nebulised hypertonic saline (HS) could reduce the duration of hospitalisation and alter the course of the illness. A Cochrane review concluded that nebulised 3% HS may significantly reduce the duration of hospitalisation and may improve the clinical severity score in infants with acute viral bronchiolitis. Included studies were undertaken using a range of therapies and comparators in a range of health-care settings. The majority of studies used 3% and 6% HS with and without a bronchodilator, with the control arm often involving nebulised normal saline (NS) with or without a bronchodilator. NS is sometimes thought to positively affect clinical outcomes and so could be considered an active comparator; older studies using distilled water as a comparator have been criticised because hypo-osmolar water could induce bronchospasm. When interpreting these studies it is important to consider that the term 'acute bronchiolitis' is used to describe phenotypically different patients in various areas of the world. The UK, Australia and a number of other countries use the definition in which widespread crackles are a characteristic, whereas in the USA and other countries it is defined by the first episode of wheezing with an apparent viral infection. Although all these patients have very similar underlying pathology, dominated by neutrophil influx into the airway, the second definition would include infants experiencing a first viral exacerbation of asthma.

In response, the hypertonic Saline in Acute Bronchiolitis Randomised controlled trial (RCT) and Economic evaluation (SABRE) study randomised infants requiring oxygen therapy for acute bronchiolitis to receive usual care or usual care with 4 ml nebulised 3% HS every 6 hours until they were fit for discharge. As a number of RCTs had been published since the last update of the Cochrane review, a systematic review was undertaken to put the trial in context.

## Objectives

### *The SABRE study*

The purpose of the SABRE study was to evaluate the clinical effectiveness of nebulised HS in the treatment of acute bronchiolitis. The primary objective of the study was to assess whether or not the addition of nebulised 3% HS to usual supportive care resulted in a reduction in time to being declared 'fit for discharge'. Secondary objectives included an assessment of the impact of the intervention on other clinical outcomes and the quality of life of infants and carers at 28 days post randomisation and an investigation of the impact on outcomes between those infants with human RSV infection and those with acute bronchiolitis due to other causes, including other viruses (non-RSV).

### *Health economics*

The objective of the health economics component was an assessment of the economic impact of the intervention on both the NHS and parents at 28 days post randomisation.

### *Systematic review*

The objective of the systematic review was to put the SABRE study in context with other controlled trials of nebulised HS for infants hospitalised with primary acute bronchiolitis, including an assessment of heterogeneity.

## Methods

### *The SABRE study*

The trial was a parallel-group, pragmatic RCT in 10 UK hospitals. The hypothesis was that the intervention would result in a 25% reduction in the primary outcome expressed as a hazard ratio (HR), the time to when infants were assessed as being 'fit for discharge', defined as in air with saturations of > 92% for 6 hours. Secondary outcomes included actual time to discharge from randomisation [length of stay (LoS)], admission to ICU/high-dependency unit (HDU), readmissions within 28 days, duration of respiratory symptoms within 28 days, infant and parental quality of life using the Infant Toddler Quality of Life Questionnaire (ITQoL) at 28 days following randomisation and adverse events (AEs). Analysts were blind to allocation.

### *Health economics*

The costs included in the analysis related to LoS by type of ward, readmissions, use of nebulised saline and, in primary care, general practitioner contacts, NHS Direct contacts, and attendances at NHS walk-in centres, minor injury units and emergency departments. Quality-adjusted life-years (QALYs) were estimated using an existing utility decrement derived for hospitalisation in children, together with the time spent in hospital derived from the data of the SABRE study. A cost-utility analysis was undertaken from the NHS perspective with a time frame of 36 days post randomisation. This was supplemented with a cost-consequences analysis (CCA), which considers the secondary clinical outcome measures alongside costs.

### *Systematic review*

The electronic databases searched included MEDLINE (via Ovid) (1946 to January 2015), EMBASE (1974 to January 2015), the Cochrane Central Register of Controlled Trials, Google Scholar (Google, Mountain View, CA, USA) (2010 to January 2015) and Web of Science (2010 to January 2015). The following trial registries were searched, using the terms 'bronchiolitis' and 'hypertonic saline', to identify any unpublished data: ClinicalTrials.gov; UK Clinical Trials Gateway; Centre for Reviews and Dissemination databases (Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database, Health Technology Assessment Database); controlled-trials.com; centrewatch.com; and National Research Register. We also hand-searched the journals *Chest*, *Paediatrics* and *Journal of Paediatrics* in January 2015 using the terms 'hypertonic saline' and 'bronchiolitis'. The reference lists of all eligible trial publications were checked to identify any further

published trials. All searches were performed between January 2013 and January 2015. We included randomised or quasi-randomised trials which compared HS and either NS (with or without adjunct treatment) or no treatment. Two reviewers extracted data to calculate mean differences (MDs), length of hospital stay (primary outcome), clinical severity scale (CSS) score and AEs with 95% confidence intervals (CIs). Meta-analysis was undertaken in RevMan version 5.2 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata version 12 (StataCorp LP, College Station, TX, USA) using both fixed- and random-effect models. We assessed statistical heterogeneity using the  $I^2$  statistic. The Cochrane risk of bias tool was used to assess the potential for systematic error within individual studies. Standard methods were used to assess the risk of outcome reporting bias and a funnel plot was generated to explore the possibility of publication bias.

## Setting

Participants were recruited from paediatric wards and assessment units from the 10 participating centres between October 2011 and December 2013.

## Participants

### *Randomised controlled trial and economic analysis*

Previously healthy infants, aged less than 1 year, admitted to hospital with a clinical diagnosis of acute bronchiolitis and requiring supplemental oxygen therapy on admission were consented and randomised within 4 hours of admission. The following were excluded: wheezy bronchitis or asthma; gastro-oesophageal reflux; previous lower respiratory tract infections; risk factors for severe disease; carer who was not fluent in English where translation services were not available; and need for admission to HDU or ICU at the time of recruitment.

### *Systematic review*

Controlled trials involving children up to the age of 2 years who had been hospitalised as the result of an episode of acute bronchiolitis.

## Interventions

### *Randomised controlled trial and economic analysis*

Randomisation was to standard supportive care with oxygen as required, minimal handling and fluid administration as appropriate to the severity of the disease, 3% nebulised HS approximately every 6 hours.

### *Systematic review*

Studies evaluating nebulised HS with or without an adjunct bronchodilator treatment given versus NS or no intervention (control) with the following pre-specified subgroups:

1. nebulised HS alone versus NS
2. nebulised HS plus a bronchodilator (e.g. salbutamol) versus NS
3. nebulised HS plus a bronchodilator (e.g. salbutamol) versus NS plus same bronchodilator
4. nebulised HS alone or plus a bronchodilator (e.g. salbutamol) versus no intervention.

## Results

### *The randomised controlled trial*

The trial recruited to target when 158 infants were randomised to HS ( $n = 141$  analysed) and 159 to standard care ( $n = 149$  analysed). There was no difference between the two arms in the time to being declared fit for discharge (HR 0.95, 95% CI 0.75 to 1.20) or to actual discharge (HR 0.97, 95% CI 0.76 to 1.23).

The median [interquartile range (IQR)] time until the infant was fit for discharge was 76.6 hours (IQR 46.1–113.3 hours) in the HS group and 75.9 hours (IQR 45.5–21.0 hours) in the standard care group. The median time until actual discharge was 88.5 hours (IQR 51.6–120.9 hours) in the HS group and 88.7 hours (IQR 50.9–123.6 hours) in the control group. Infants who were RSV positive ( $n = 179$ , median 80.7 hours) took longer to be fit for discharge than RSV-negative children ( $n = 27$ , median 50.8 hours, HR 1.94, 95% CI 1.24 to 3.02 hours;  $p = 0.004$ ), and somewhat longer to be actually discharged (median 91.1 hours vs. 72.2 hours, HR 1.47, 95% CI 0.95 to 2.28 hours;  $p = 0.09$ ), but we found no evidence of an interaction between viral status and treatment effect. Differences in routine practice between centres meant that viral testing was not undertaken in 79 patients.

There was no difference between treatment groups in the numbers admitted to HDU/ICU or readmitted within 28 days of randomisation. We observed no important differences in score on any of the ITQoL dimensions. There was no difference between groups in the number or severity of observed AEs. Six AEs were possibly related to saline treatment. These included one serious adverse event (SAE), bradycardia and desaturation during administration of the nebuliser, which had resolved by the following day. The remaining five non-SAEs, each of which were observed in separate subjects, were bradycardia (self-correcting), desaturation, coughing fit and increased respiratory rate (all of which were resolved within 1 day), and a chest infection which resolved after 6 days.

### *Health economics*

When individual cost components are combined with their unit costs, the mean hospital costs were £2595 and £2727 for the control and the intervention groups, respectively. The 95% CI around the difference of £132 is –£520 to £785. QALYs were 0.0000175 greater in the intervention group but the difference was not statistically significant. Mean primary care costs for available patients were £19 and £11 in the control and the intervention groups, respectively. The difference in means was £8 (95% CI –£21 to £6;  $p = 0.25$ ). Given the large number of missing data, it was decided not to impute missing values or combine them with the hospital costs. With numerically higher costs (£132) and QALYs (0.0000175), the incremental cost-effectiveness ratio is approximately £7.6M per QALY gained. One-way sensitivity analyses examining different unit costs for time spent on a ward, ICU or HDU did not alter the probability that nebulised saline would be cost-effective. Across all the measures considered within the CCA, there is only one statistically significant difference between the study arms, relating to the family cohesion domain of the ITQoL. Given the uncertainties and biases associated with this result, the robustness of this difference is open to question.

### *Systematic review*

In 15 trials ( $n = 1922$ ), HS reduced mean LoS by –0.36 days (95% CI –0.50 to –0.22 days). Risk of bias and high levels of heterogeneity ( $I^2 = 78\%$ ) in the main analysis and one out of four intervention subgroups suggest that the result should be treated cautiously. A reduction in CSS (five trials,  $n = 516$ , MD –1.36, 95% CI –1.52 to –1.20) should also be treated cautiously. None of the trials reported intervention-related SAEs.

Five trials ( $n = 385$ ) combined HS with adrenaline and found a clinically important, statistically significant difference compared with adrenaline alone (MD –0.61, 95% CI –0.94 to –0.28;  $p = 0.578$ ;  $I^2 = 0\%$ ).

## Conclusions

### *The SABRE study*

The addition of nebulised HS to good supportive care when treating infants admitted to hospital with acute bronchiolitis does not appear to cause any harm but confers no benefit.

### *Health economics*

The economic analysis used two forms of analysis to consider the cost-effectiveness of nebulised HS in this patient population. The cost–utility analysis suggests that the intervention cannot be considered cost-effective. Taking a broader view of benefits that includes any of the primary and secondary outcomes measures does not appreciably alter this conclusion.

### *Systematic review*

The systematic review suggests that there is too much heterogeneity to make a pooled estimate of effect across thirteen studies of inpatient care a useful basis for decision-making, and it shows that large studies, and those from northern Europe, have negative results which support the findings of the SABRE study.

## Future work

Potentially beneficial interventions such as high-flow oxygen therapy and others to be identified in the future should be subject to high-quality randomised trials before any recommendations regarding practice are made.

## Study registration

This study is registered as ClinicalTrials.gov NCT01469845 and PROSPERO CRD42014007569.

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