Nebulised 3% hypertonic saline versus 0.9% saline for treating patients hospitalised with acute bronchiolitis: protocol for a randomised, double-blind, multicentre trial

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ABSTRACT

Introduction Bronchiolitis is an acute viral infection of the lower respiratory tract. It is most commonly caused by respiratory syncytial virus. Being a common reason for hospitalisation, it affects 13–17% of all hospitalised children younger than 2 years old. It is more prevalent among children younger than 2 years who are hospitalised due to respiratory distress (rales (crackles) with or without wheezing), and the presence of auscultation findings (rales (crackles) with or without wheezing). A total of 140 children will be randomised (1:1) to receive either hypertonic saline nebulisation (5 mL, three times a day) or normal saline at the same dose. The primary outcome measure will be the duration of hospitalisation.

Methods and analysis This will be a randomised, double-blinded, parallel-group, controlled trial. Children younger than 2 years who are hospitalised due to bronchiolitis will be recruited from at least three paediatric departments in Poland. Bronchiolitis is defined as an apparent viral respiratory tract infection associated with airway obstruction that is manifested by at least one of the following symptoms: tachypnoea, increased respiratory effort, crackles and/or wheezing. A total of 140 children will be randomised (1:1) to receive either hypertonic saline nebulisation (5 mL, three times a day) or normal saline at the same dose. The primary outcome measure will be the duration of hospitalisation.

Ethics and dissemination The Bioethics Committee of the Lower Silesia Medical Chamber in Wroclaw approved the study protocol (4/PNDR/2023). Caregivers will receive oral and written information about the study and written informed consent will be obtained by the study physicians. The findings of the study will be submitted to a peer-reviewed journal, and abstracts will be submitted to relevant national and international conferences.

Trial registration number ClinicalTrials.gov Registry (NCT06069336).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A randomised controlled trial is the most robust methodology to assess the effectiveness of therapeutic interventions.
⇒ A multicentre study allows quicker recruitment, diverse population coverage and greater generalisability.
⇒ Commonly used non-evidence-based interventions may delay recruitment and bias trial results.

INTRODUCTION

Bronchiolitis is an acute viral infection of the lower respiratory tract. It is most commonly caused by respiratory syncytial virus (RSV). More than 60% of children are infected by this virus by 1 year of age and more than 90% of children are infected by 2 years of age. Other viruses, such as rhinovirus, human metapneumovirus, influenza, parainfluenza and adenovirus, can cause bronchiolitis as well. Diagnosis is based on clinical symptoms. Different criteria used in different regions lead to difficulties in comparing research and recommendations internationally. The diversity concerns age (<12 or <24 months), the presence of auscultation findings (rales (crackles) with or without wheezing), and first or subsequent episodes. There are distinct phenotypes of the disease described, and there is an ongoing discussion about the need to introduce a new definition.

Bronchiolitis is a common reason for hospitalisation. It affects 13–17% of all hospitalised children younger than 2 years old. The median length of hospital stay (LOS) for children with bronchiolitis is 3 days; however, up to 5.6% of hospitalised children need intensive care unit admission. The mortality rate of bronchiolitis is 2.8 per 100 000 persons.
Despite differences in definitions, recommendations published over recent years are mostly consistent with regard to the treatment method.\textsuperscript{2,8,9} Only supportive therapy is recommended. Standard therapy includes suctioning nasal secretions, water-electrolyte balance maintenance and oxygen supplementation when needed. Evidence suggests no benefit with the use of inhaled bronchodilators, nebulised epinephrine, or nebulised and systemic steroids.\textsuperscript{28-10} The clinical reality is different from the recommendations, and many studies describe non-adherence to the recommendations and the use of non-evidence-based diagnostic and therapeutic approach.\textsuperscript{11}

Although 0.9% normal saline (NS) inhalation is not recommended as a supportive treatment, it is commonly used in our country to treat children with bronchiolitis and has the status of being a supportive treatment.

A study published in 2002 by Sarrell \textit{et al} triggered a series of publications assessing the effectiveness of hypertonic saline (HS) in the treatment of bronchiolitis.\textsuperscript{12} Their results have been summarised in meta-analyses.\textsuperscript{13-16} Researchers have mainly focused on three clinically relevant outcomes: impact of nebulisation of HS in emergency departments (EDs) on hospital admission rate, and for inpatients, impact on hospital LOS and reduction in the severity of respiratory distress based on Clinical Severity Score (CSS) and Respiratory Distress Assessment Instrument (RDAI) values.

A 2018 meta-analysis of eight randomised controlled trials (n=1708) showed a 16% reduction in the risk of hospitalisation among patients treated with HS compared with those treated with NS (risk ratio (RR): 0.84, 95% CI: 0.71 to 0.98, p=0.03). A significant effect of HS in reducing the risk of hospitalisation was found only in the subgroup analyses of trials in which HS was mixed with bronchodilators and multiple doses (≥3) were given.\textsuperscript{13}

A 2020 meta-analysis of 32 publications (n=4186) found that compared with the control group, the HS group exhibited significant reduction in the severity of respiratory distress. This meta-analysis included studies that used the CSS (mean difference (MD) −0.71; 95% CI −1.15 to −0.27) and full stop after RDAI (MD −0.60; 95% CI −0.95 to −0.26) for evaluation. Further, the HS group had a decreased hospital LOS of 0.54 days (MD −0.54; 95% CI −0.86 to −0.23).\textsuperscript{15}

A 2021 updated meta-analysis by Heikkilä and Korppi (n=2350) revealed that MD in LOS between HS cases and controls was not statistically significant, with a difference of −0.30 days (95% CI −0.66 to 0.05).\textsuperscript{16}

The most recent 2023 meta-analysis of 34 publications (n=5205) found that hospitalised infants treated with nebulised HS had a shorter mean LOS compared with those treated with nebulised NS or standard care (MD −0.40 days, 95% CI −0.69 to −0.11).\textsuperscript{14} Infants who received HS also had lower post-inhalation clinical scores than infants who received NS in the first 3 days of treatment (day 1: MD −0.64, 95% CI −1.08 to −0.21; day 2: MD −1.07, 95% CI −1.60 to −0.53; day 3: MD −0.89, 95% CI −1.44 to −0.34). All results were assessed as showing low-certainty evidence. Nebulised HS was found to reduce the risk of hospitalisation by 13% in infants who were outpatients compared with those treated in the ED (RR 0.87, 95% CI 0.78 to 0.97). There were only minor and spontaneously resolved adverse events from the use of nebulised HS when given with treatment to relax airways (bronchodilators).

In the studies analysed in this meta-analysis, salbutamol (12 trials) and epinephrine (5 trials) were used, despite many recommendations against the use of these drugs in bronchiolitis management. Only three trials conducted in paediatric departments compared HS alone with NS.\textsuperscript{14}

A 2015 study by Silver \textit{et al}, which was not included in the above-mentioned meta-analysis due to the inclusion of infants with a history of wheezing, was carried out in 277 hospitalised children with bronchiolitis, who were randomised to receive 4mL nebulised HS every 4 hours from enrolment until hospital discharge or nebulised NS at the same dose. There were no significant differences in hospital stay between the groups (−2.0 (1.3–3.3) and 2.0 days (1.2–3.0), respectively, p=0.96).\textsuperscript{17}

Inclusion in most of the published studies was limited to the first episode of disease and infants younger than 12 months old. From a practical point of view, there is no reason to not diagnose bronchiolitis in children several months old admitted to the hospital with a second episode showing the typical symptoms of an RSV.

Observing the evolution of meta-analysis results as studies become available has led us to design a multicentre study. Taking into consideration the differences between countries and recommendations, the lack of a common definition and the practical aspect of the study, we have decided to use a broad definition of bronchiolitis including children up to 24 months old with all auscultation findings (wheezes and crackles), which are not limited to the first episode.

Taking these together, we have decided to perform a real-life pragmatic study evaluating commonly used interventions.

**Trial objectives and hypotheses**

The main objective of this trial is to assess the impact of nebulised HS on LOS in patients hospitalised with bronchiolitis. We aim to conduct a well-designed study with sufficient power, an adequate follow-up period and relevant clinical outcomes.

**METHODS AND ANALYSIS**

The trial is registered at http://www.clinicaltrials.gov (NCT00669336), and any important changes in the protocol will be implemented there.

**Study design**

This study is designed as a randomised, double-blinded, parallel-group, controlled trial, with an allocation of 1:1. The study design is described in more detail in subsequent sections.
Setting and participants
Recruitment will take place at three paediatric departments in Poland: St Hedwig of Silesia Hospital in Trzebnica, Sokolowski Hospital in Walbrzych and Medical University of Warsaw. The involvement of other recruiting sites is under consideration, provided that the study staff are experienced, adequately trained and competent in conducting clinical trials. The start of the recruitment period is planned to occur in October 2023 and should be completed within the next 2 years. Participants will be randomised within 12 hours after admission to the hospital. Caregivers will receive oral and written information about the study. Written informed consent will be obtained by the study physicians. The consent form is available in the online supplemental material.

Inclusion criteria
Children eligible for the trial must fulfil all of the following criteria:
1. Children admitted to the hospital with the clinical diagnosis of acute bronchiolitis, which is defined as an apparent viral respiratory tract infection associated with airway obstruction manifested by at least one of the following symptoms:
   1. Tachypnoea (WHO definition).
   2. Increased respiratory effort manifested as follows:
      - Nasal flaring.
      - Grunting.
      - Use of accessory muscles.
      - Intercostal and/or subcostal chest wall retractions.
      - Apnoea.
   3. Crackles and/or wheezing.
2. Aged 5 weeks–24 months old.
3. A caregiver must provide written informed consent.

Exclusion criteria
1. Infants hospitalised with severe bronchiolitis (requiring mechanical ventilation or intensive care, or oxygen saturation <85% on room air).
2. History of prematurity (gestational age <34 weeks).
3. Diagnosis of a clinically significant chronic disease (cardiac, respiratory, neuromuscular or metabolic).
4. Immunodeficiency.
5. Gastro-oesophageal reflux.
6. Diagnosis or suspicion of asthma.
7. Inhaling a nebulised 3% HS solution within 12 hours before enrolment.
8. Inhaling bronchodilators within 24 hours before enrolment.
9. Inhaling steroids within 24 hours before enrolment.
10. Systemic steroid therapy in the preceding 2 weeks.

Interventions
The intervention under investigation is nebulised 3% HS (NEBU-dose hypertonic), and the comparator is 0.9% NA (NEBU-dose isotonic). Both are produced by Manufacturing, SL and are used in standard hospital practice. The treatment will be delivered through nebulisation using oxygen with 5 L of oxygen flow, or through a compressed air-driven jet nebuliser (PARI Boy Junior) every 6 hours for three times a day with a night break, until discharge. Nebulisation will be performed by trained study nurses or by parents under the supervision of a nurse.

Supportive care will be similar for both groups. Standard therapy includes suctioning nasal secretions, water–electrolyte balance maintenance and oxygen supplementation when needed. Oxygen therapy will be administered using nasal prongs or a mask at an oxygen saturation level ≤92% on room air. If standard subnasal supplemental oxygen fails in hypoxic infants, we will use a high-flow nasal cannula (HFNC). All activities will be recorded in the medical records. Table 1 presents a timetable of the activities planned during the study.

All patients will be enrolled within 12 hours upon admission to the hospital. The decisions to discharge the patients will be carried out at morning rounds by the attending physician, based on clinical grounds alone. At any time, caregivers will have the right to withdraw their participating child from the study; they will not be obliged to give reasons for this decision, and there will be no effect on subsequent physician and/or institutional medical care.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Study timetable</th>
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<tr>
<td>Activity</td>
<td>Admission day</td>
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<td>Inclusion/exclusion criteria</td>
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<td>Informed consent</td>
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<td>Enrolment</td>
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<td>Randomisation</td>
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<tr>
<td>Clinical Severity Score according to Wang Scale and RDAI</td>
<td>x</td>
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<tr>
<td>Intervention: hypertonic saline or normal saline nebulisation</td>
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<tr>
<td>Follow-up</td>
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<td>Adverse events</td>
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RDAI, Respiratory Distress Assessment Instrument.
Concomitant medications
The concomitant administration of any other medication, including antipyretics and antibiotics, will be at the discretion of the attending physician to provide adequate care. In the event of clinical worsening, the healthcare provider will have the option of giving an additional treatment. However, it is recommended that no unnecessary concomitant medication be used. In particular, the use of inhaled bronchodilators, systemic and inhaled steroids, and nebulised epinephrine should be avoided. Administration of the aforementioned drugs will be recorded and classified as a protocol violation.

Follow-up
All study participants will be followed up for the duration of hospitalisation and then for an additional 7 days (phone contact) to collect adverse events and assess the readmission rate.

Outcomes
The primary outcome will be the LOS.
Secondary outcomes will be:
- Number of participants requiring oxygen supplementation.
- For patients requiring oxygen:
  - Duration of oxygen supplementation. The time until the infant will be assessed as being ‘fit for discharge’, which is defined as the point at which the infant will be feeding adequately (taking >75% of their usual intake based on parents’ assessment) and will have satiation of at least 92% for 6 hours on room air, while the axillary body temperature will remain below 37°C for at least 24 hours.
- Readmission rate within 7 days after discharge.
- Adverse events, especially incidence of acute otitis media and pneumonia.
- Worsening of clinical status, including the following: Paediatric intensive care unit admission. The need for oxygen supplementation via HFNC. Bronchospasm within 30 min of a nebulised study treatment as indicated by an increase/worsening of the RDAI of <4 points.
- Value of CSS (RDAI and Wang Scale) 30 min after intervention and 24 hours, 48 hours and 72 hours after enrolment.

Randomisation
A computer-generated randomisation list will be prepared by a staff member with no clinical involvement in the trial using a computer program (StatsDirect), with an allocation ratio of 1:1 and a block of six.

Allocation concealment
The allocation sequence will be concealed from the researchers by enrolling and assessing participants in a sequential way using white, opaque, sealed and stapled envelopes, which will be opened only after obtaining parental/caregiver-informed consent and registering the basic demographic data to the case report form (CRF). Consecutive randomisation numbers will be given to participants at enrolment. The study products will be packaged as product A or product B, and will be given according to the randomisation list.

Blinding
The study products (3% sodium chloride (NaCl) and 0.9% NaCl) will be packaged in identical bottles. Their contents will look the same. The researchers, caregivers, outcome assessors and the staff member responsible for the statistical analysis will be blinded to the intervention until the completion of the study. The information on intervention assignments will be stored in a sealed envelope in a safe place at the administrative part of the department. The personal information of potential and enrolled participants will be stored in a locker at the study site, which is accessible for the involved researchers only.

Compliance
Compliance with the study protocol will be checked via analysis of the medical records. Based on previously published trials, it seems to be appropriate to consider participants receiving <75% of the recommended doses as non-compliant.

Power calculation
The primary outcome of the study is the hospital LOS. Based on available data in the literature, the average duration of hospitalisation is 3 days. An analysis of hospital records showed that the mean duration of hospitalisation due to bronchiolitis at our departments is 3.5 days. Based on the literature data, we assume that a reduction in the hospital LOS by 0.6 day will show a clinically significant difference in the effectiveness of nebulised HS versus NS. To detect such a difference in the hospital LOS between the study groups with a power of 90% and α=0.05, a sample of 116 children is needed. Assuming that the rate of loss to follow-up is approximately 20%, we aim to recruit a total of 140 children for this study. There were similar numbers of recruited patients in recently published studies.

At the Department of Paediatrics of St Hedwig of Silesia Hospital, there are 150 admissions of children with bronchiolitis per year. Assuming that 30% of these children will be eligible for this study, we will achieve adequate participant enrolment to reach the target sample size during the 2 years of recruitment. There are similar admission rates at Wałbrzych and Warsaw Hospitals.

Data collection and management
All study participants will be assigned a study identification number. CRFs will be completed on paper forms. Data will then be entered and stored in a password-protected electronic database. The original paper copies of the CRFs and all study data will be stored in a locker at the study site, which is accessible for the involved researchers only.
Statistical analysis
All analyses will be conducted on an intention-to-treat basis, including all patients in the groups to which they are randomised and for whom outcomes are available (including dropouts and withdrawals). Descriptive statistics will be used to summarise baseline characteristics. The Student’s t test will be used to compare the mean values of continuous variables with a normal distribution. For non-normally distributed variables, the Mann-Whitney U test will be used. The χ2 test or Fisher’s exact test will be used, when appropriate, to compare percentages. For continuous outcomes, differences in means or differences in medians (depending on the distribution of the data), and for dichotomous outcomes, the RR and number needed to treat, all with a 95% CI, will be calculated. The difference between the study groups will be considered significant when the p value is <0.05, when the 95% CI for RR does not include 1.0, or when the 95% CI for MD does not include 0. All statistical tests will be two tailed and performed at the 5% level of significance.

Monitoring
This study will be carried out in accordance with the approved protocol. Both isotonic and hypertonic saline are being safely used worldwide. An independent Data and Safety Monitoring Board (DSMB) will be set up prior to the start of the study. The DSMB will review data after recruitment of 25%, 50% and 75% of participants to review study progress and all adverse events.

Harms
Although the occurrence of adverse events as a result of participation in the current trial is not expected, data on adverse events data will be collected. All serious adverse events will be immediately reported to the study coordinators, who will be responsible for notifying the Ethics Committee, all participating investigators and the manufacturer of the study products.

Auditing
The Ethics Committee did not require auditing for this study.

Patient and public involvement
None.

ETHICS AND DISSEMINATION
The Bioethical Committee of the Lower Silesia Medical Chamber in Wroclaw issued the approval for this study before the commencement of recruitment (approval number 4/PNDR/2023). Caregivers will receive oral and written information about the study and written informed consent from the caregiver will be obtained by the study physicians. Any modifications to the protocol that may affect the conduct of this study will be presented to the Bioethical Committee. The findings of the study will be submitted to a peer-reviewed journal, and abstracts will be submitted to relevant national and international conferences.

Contributors
HS conceptualised the study. SS developed the first draft of the manuscript. HS, SS and AB contributed to the development of the study protocol and approved the final draft of the manuscript.

Funding
This study will be fully funded by the Department of Paediatrics, St Hedwig of Silesia Hospital, Trzebnica, Poland.

Competing interests
None declared.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Parental/guardian consent obtained.

Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
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REFERENCES


INFORMED CONSENT FORM

Title of the study: "Nebulised 3% Hypertonic Saline Versus 0.9% Saline for Treating Patients Hospitalized With Acute Bronchiolitis"

I received information about this study and had my first conversations with the doctor conducting the study. I have read and understood the information contained in the patient information and informed consent form. I had the opportunity to ask questions and all my questions were answered satisfactorily. I had enough time and opportunity to ask detailed questions about the study and to make decisions regarding my child's participation in the study.

I voluntarily consent to my child's participation in this study and may withdraw my child from the study without giving any reason at any time. During this examination, I consent to members of the medical staff being able to contact my child's family doctor and other health care professionals to obtain access to my child's medical history during the examination and to conduct the examination by protocol.

I was informed that I would receive a signed and dated copy of this document.

__________________________
Name and surname (in capital letters) of the study participant

__________________________
Name and surname (in capital letters) of the parent/legal guardian. Relationship

__________________________
Signature of parent/legal guardian Date of signature

CONSENT FORM FOR THE PROCESSING OF PERSONAL DATA

In addition, I consent to the use and management of my child's data in the manner described in this patient information and the informed consent form by institutions and persons involved in the study, by the provisions of Polish and EU law on the protection of personal data, including by the provisions of Act of August 29, 1997, on the protection of personal data (Journal of Laws of 1997, No. 133, item 883, as amended) and European Union Directive 95/46/EC.

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Name and surname (in capital letters) of the study participant

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Name and surname (in capital letters) of the parent/legal guardian.

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Signature of parent/legal guardian Date of signature

RESEARCHER OBTAINING CONSENT

__________________________
Name and surname (in capital letters) Investigator's signature Date of signature