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Effectiveness of nebulized hypertonic saline in mild-to-moderate bronchiolitis

Submission date
07/11/2024

Recruitment status
Recruiting

Registration date
08/11/2024

Overall study status
Ongoing

Last Edited
08/05/2025

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This clinical trial is being conducted in young children and infants with bronchiolitis, a common lung infection characterized by swelling, irritation and mucus accumulation within the lungs that causes symptoms similar to those of the common cold. Although typically non-serious, it can cause coughing, wheezing (whistling sound when breathing) and difficulty in breathing that may lead to hospitalization. The present trial aims to evaluate the efficacy and safety of a nebulized hypertonic saline solution (Sinomarin® Babies; investigational product) in children with mild-to-moderate disease aged 1 to 24 months. A nebulized isotonic saline solution will be used as a comparator. Both products are approved medical devices that are commonly used in various respiratory conditions, including bronchiolitis. While the isotonic solution contains 0.9% salt (similar to the physiological salt concentration in body fluids), the hypertonic solution has a higher salt concentration, 2.3%. Both solutions are expected to reduce lung edema and mucus buildup up reducing symptom severity in patients. During the trial, and in addition to the nebulized saline solutions, all patients will receive appropriate medical treatment and ongoing care as per applicable disease treatment standards.

Who can participate?
Previously healthy children aged 1 to 24 months who are visiting the Emergency Room (ER) and Day Care Department (DCD) of the Srebrnjak Children’s Hospital in Zagreb, Croatia, with a first episode of wheezing

What does the study involve?
Recruitment within the study will take place upon completion of certain regular exams that ascertain that the assigned inclusion and exclusion criteria are satisfied. These exams include physical examination, vital signs, measurement of body temperature, blood oxygen saturation and assessment of the severity of the child's disease (lung function). Following consent to participate in the study, the children will receive the investigational medical device for the first time or the comparator in addition to standard treatment. A device for measuring lung function (Ventica®) may also be proposed by the Investigator. The device will be used to measure and record the parameters of the child's breathing during sleeping, on the 1st, 4th, and 6th night of his/her participation in the study.

Following the 1st visit, all study participants will return to the hospital daily for the next 6 days. For the first 5 days, at each visit, the child will receive the same hypertonic or isotonic saline solution, depending on which group he/she was initially assigned to. On the last day, day 7, the final visit will occur, and therapy will be applied only if necessary. At each visit, the doctor will perform a physical exam and measure pulse and blood oxygen saturation. In addition, if necessary, the content of the child's nose will be sucked to clear the airways, and according to the assessment of the Investigator, he or she will also receive standard prescribed therapy.

On the 1st visit, the Investigator will provide a sufficient number of vials of the saline products for a total of 6 days of home treatment. The parents are expected to give the nebulized saline solution to the child 2 times a day (in addition to the dose he/she will receive at the hospital). All used and unused packaging of the products will be returned at the last visit. Finally, the Investigator will provide a treatment diary to record information about giving the products to the child at home, using the mentioned Ventica® electronic device, giving other medications according to the doctor's instructions and a few basic observations about the child's disease. The electronic device will also be returned to the Investigator on the last visit, who will extract the necessary information from it.

One week after the last visit, if there is no reason for the child to visit the day hospital again or the emergency room, a study-participating doctor from the trial team will contact the trial participants for a final follow-up call. At the end of the study, and once all data is collected, an evaluation of the efficacy and safety of the investigational device versus the comparator will be performed. This will include assessment of improvement of clinical disease scores and additional factors, including discharge rates, rates of hospital revisits, burden of illness and frequency of adverse events.

What are the possible benefits and risks of participating?
These results will help to collect data on the most appropriate nebulized saline treatment used in bronchiolitis patients together with standard medication. In terms of safety, although it is impossible to determine risks in advance, the potential side effects of the investigational medical device and the comparator are the same and include possible mild irritation of the mucosa and increased nasal secretion at the beginning of use. For the study subjects using the Ventica® device, the device electrodes may cause temporary local skin irritation at the site of application. Overall, based on prior use experience with nebulized saline solutions, the safety risk is low.

Where is the study run from?
Gerolymatos International SA, Greece

When is the study starting and how long is it expected to run for?
March 2023 to May 2026

Who is funding the study?
Gerolymatos International SA, Greece

Who is the main contact?
Prof Mirjana Turkalj, mturkalj@bolnica-srebrnjak.hr

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
SB-BRO-01, CIV-ID: CIV-23-07-043616

Study information

Scientific Title
Effectiveness of nebulized mild hypertonic saline solution in children with mild-to-moderate RSV bronchiolitis: randomized, open-label, active-control intervention study

Acronym
HYPERBRO

Study objectives
Bronchiolitis, a common viral infection affecting the lower respiratory tract in children under two years of age, leads to significant morbidity and mortality. Despite the high prevalence of the disease, there is no universally recognized evidence-based treatment approach. Options for treatment encompass bronchodilators, epinephrine, corticosteroids and isotonic/hypertonic saline. Nebulized hypertonic saline of 3% NaCl is specifically recommended for hospitalized infants and children with bronchiolitis (Evidence Quality: B; Recommendation Strength: Weak Recommendation [based on randomized controlled trials with inconsistent findings])) as per the latest guidelines. In this study, the specific effectiveness of an approved hypertonic solution of 2.3% NaCl commonly used in other respiratory conditions will be evaluated in patients with mild-to-moderate bronchiolitis. The product -to be administered via nebulization- will be compared to nebulization of 0.9% NaCl to determine superiority. The main objective of this study is to assess improvement of clinical scores and additional factors including discharge rates, rates of hospital revisits, burden of illness and frequency of adverse events in the two groups.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 19/05/2023, Central Ethics committee, Agency for Medical Products and Medical Devices of Croatia (Ksaverska cesta 4, Zagreb, 10000, Croatia; +38514884100; halmed@halmed.hr), ref: Class: 530-04/23-03/24; order number: 381-14-09/21-23-05

2. approved 04/04/2024, Central Ethics committee, Agency for Medical Products and Medical Devices of Croatia (Ksaverska cesta 4, Zagreb, 10000, Croatia; +38514884100; halmed@halmed.hr), ref: Class: 530-04/23-03/24; order number: 381-14-09/389-24-08

Study design
Single-center randomized open-label active-controlled trial with a parallel design

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Mild-to-moderate RSV (respiratory syncytial virus) bronchiolitis

Interventions
The study interventions will include:
- Investigational medical device: Sinomarin® Babies single use vials, hypertonic saline (2.3 % NaCl), 5 mL, nebulized inhalations.
- Comparator medical device: Physiodose, 0.9 % NaCl, 5 mL vials, Laboratoires Gilbert, nebulized inhalations.
Both medical device products have marketing authorization in the EU.

Patients with mild to moderate RSV bronchiolitis (Wang score 3-8) will be randomized in two groups:
Group 1: Infants receiving standard nebulized medication and nebulized 0.9 % NaCl (Physiodose)
Group 2: Infants receiving standard nebulized medication and nebulized 2.3 % NaCl (Sinomarin Babies)

A block randomization method will be used to stratify patients into blocks of 3 each, each comprising of 3 patients. The 2:1 sequence of administration will be assigned to the subject by randomization module implemented to the study eCRF.

Treatments will be administered as follows:
Day 1: 2 hospital nebulization sessions and 2 home nebulization sessions
Days 2-6: 1 hospital nebulization session and 2 home nebulization sessions
Day 7: treatment as needed

Each nebulization comprises a first nebulization of standard medication (bronchodilator) followed by saline nebulization.

Intervention Type
Device

Phase
Phase III/IV

Drug/device/biological/vaccine name(s)
Investigational Medical Device (IMD): Sinomarin® Babies single use vials, hypertonic saline (2.3 % NaCl), 5 mL, nebulized inhalation. Comparator Medical Device: Physiodose, 0.9 % NaCl, 5 mL vials, Laboratoires Gilbert, nebulized inhalation. Non-Investigational Medicinal Products (nIMPs): Bronchodilators (salbutamol or racemic epinephrine), inhaled corticosteroids (budesonide) or parenteral corticosteroids (methylprednisolone), antipyretics (paracetamol or ibuprofen). In case of developing concomitant pneumonia: antibacterial medications (cephalosporine antibiotics, beta-lactam antibiotics, or macrolide antibiotics). If necessary: nasal suction, oxygen therapy, rehydration (intravenous saline or glucosaline).

Primary outcome(s)
The severity of bronchiolitis measured using the Wang Clinical Severity Score (WBSS) each day and from baseline to day 3

Key secondary outcome(s))
Current secondary outcome measures as of 15/11/2024:
1. Changes in the following parameters were recorded from Baseline to Day 1 (i.e. after 2 h): clinical severity score using Wang Clinical Severity Score (WCSS) measurements, temperature using a thermometer, respiratory rate measured by recording the number of breaths per minute, SpO2 determined by pulse oximetry and heart rate measured with a heart monitor.
2. Changes in the following parameters were recorded from Baseline to Day 7: clinical severity score using Wang Clinical Severity Score (WCSS) measurements, temperature using a thermometer, respiratory rate measured by recording the number of breaths per minute, SpO2 determined by pulse oximetry and heart rate measured with a heart monitor.
3. Discharge and hospital admission rates were recorded after 2 h of observation of Day 1 and over the complete 7-day treatment period
4. Persistent cough, number of unscheduled visits and number of lost days of work of caregivers were recorded during the complete 7-day treatment period
5. Adverse events number, severity, and association with treatment were recorded during the complete 7-day treatment period
6. Expiratory variability index (EVI) measurements using the Ventica® device as recorded overnight on Days 1 to 2, Days 4 to 5 and Days 6 to 7.

Previous secondary outcome measures:
1. Changes in clinical severity score, temperature, respiratory rate, SpO2 and heart rate (Timepoint: Baseline to Day 1 i.e. after 2 h)
2. Changes in clinical severity score, temperature, respiratory rate, SpO2 and heart rate 2 (Timepoint: Baseline to Day 7)
3. Discharge rate and hospital admission rate (Timepoint: after 2 h of observation of day 1 and over the complete 7-day treatment period)
4. Persistent cough, number of unscheduled visits and number of lost days of work of caregivers (Timepoint: complete 7-day treatment period)
5. Adverse events number, severity, association with treatment (Timepoint: complete 7-day treatment period)
6. Recordal of EVI measurements using the Ventica® device (Timepoint: Day 1, Day 4, Day 6; overnight measurements extending to Day 2, Day 5 and Day 7, respectively)

Completion date
22/05/2026

Eligibility

Key inclusion criteria
Previously healthy children visiting the Emergency Room (ER) and Day Care Department (DCD) with the following inclusion criteria will be recruited:
1. Age between 4 weeks and 2 years
2. First episode of wheezing
3. History of upper viral respiratory tract infection (symptoms of coryza, cough or fever)
4. Children with mild-to-moderate disease as evaluated with the Wang score between 3 and 8

Participant type(s)

Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
4 weeks

Upper age limit
24 months

Sex
All

Key exclusion criteria
1. Any underlying disease, comorbidity or congenital malformation (e.g., cystic fibrosis, bronchopulmonary dysplasia, cardiac or renal disease, etc)
2. Prior history of wheezing or asthma
3. Children with severe disease as evaluated with the Wang score (>8)
4. Children with progressive respiratory distress requiring mechanical ventilation
5. Previous treatment with bronchodilators (within the last 4 h), steroids (within 48 h), or nebulized saline solutions (within 12 h)

Date of first enrolment
21/10/2023

Date of final enrolment
01/05/2026

Locations

Countries of recruitment
Croatia

Study participating centre
Srebrnjak Children's Hospital (Dječja bolnica Srebrnjak)
Srebrnjak 100
Zagreb
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10000

Sponsor information

Organisation
Gerolymatos International SA

Funder(s)

Funder type
Industry

Funder Name
Gerolymatos International SA

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the study will be available upon request from the study's principal investigator. Prof Mirjana Turkalj, mturkalj@bolnica-srebrnjak.hr.
• The type of data that will be shared: Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices). The data will be shared with researchers who provide a methodologically sound proposal to achieve the aims of the approved proposal. A data access/transfer agreement may apply.
• Timing for availability: After publication and 24 months following article publication.
• Whether consent from participants was required and obtained: All participants signed an informed consent form
• Comments on data anonymization: The informed consent form describes in detail the data anonymization process. The whole process is in agreement with regulations on clinical trials, local ethics regulations and GDPR provisions.
• Any ethical or legal restrictions: There are no restrictions
• Any additional comments: None

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2.0	27/02/2024	18/11/2024	No	No