The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis

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KEYWORDS
Bronchiectasis; Hypertonic saline; Isotonic saline; Airways clearance; Quality of life; Respiratory tract infections

Summary
Background and aims: Inhalation of hypertonic saline (HTS) has short term positive effects on airways clearance in non-cystic fibrosis (CF) bronchiectasis, however its long term effects are unknown. The aim of this study was to determine the effect of HTS 6% on exacerbations, quality of life (QOL) and respiratory function over 12 months in non-CF bronchiectasis.

Methods: Forty patients were randomised to inhale isotonic saline (IS) 0.9% or HTS 6% daily for 12 months. Participants recorded their symptoms in a daily diary. Quality of life and respiratory function were measured after three, six and 12 months. Number of exacerbations and changes in sputum colonisation were recorded at 12 months. Participants, assessors and clinicians were blinded to group allocation.

Results: The exacerbation rate at 12 months was similar in the two groups and similar clinically significant improvements in QOL were seen in both groups. The FEV1 increased in both groups after six months (mean 90 ml, 95% confidence interval 11–169 ml) with no difference between groups (p = 0.394). The FEF25–75% significantly improved at all time points (mean increase at 12 months 187 ml, 69–304 ml) with no difference between groups (p = 0.705). There was a reduction in sputum colonisation in both groups (p = 0.046).

Conclusions: Inhalation of HTS or IS has similar effects on exacerbations, QOL, sputum colonisation and respiratory function over 12 months in non-CF bronchiectasis. The trial was registered with both Clinical Trials.gov — NCT00484263 and Australian New Zealand Clinical Trials Registry — ACTRN12607000367448.
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Introduction

Non-cystic fibrosis (CF) bronchiectasis is a chronic lung disease characterised by permanent dilatation of the bronchi. Predominant features include chronic cough and abnormal sputum production, leading to mucus accumulation, recurrent infections and decreased lung function, which result in a significant reduction in quality of life (QOL). Airway hygiene is usually maintained by the mucociliary escalator which is influenced by both physiological factors and disease. Patients with non-CF bronchiectasis are not able to rely on this mechanism to clear their secretions and often need daily physiotherapy which has traditionally included the active cycle of breathing technique, postural drainage and positive expiratory pressure therapy.

Hypertonic saline (HTS) 4%–7% is reported to improve hydration of the airway surface and the rheology and transportability of sputum. It may also have anti-inflammatory effects. A long term randomised controlled trial demonstrated improvements in lung function and reductions in the frequency of exacerbations and antibiotic use in individuals with CF when compared to isotonic saline (IS). Whether or not the same benefits can be achieved in non-CF bronchiectasis is still to be determined. A short term crossover study showed that HTS 7% was more effective than IS in assisting with expectoration of sputum and can safely be used in non-CF bronchiectasis, however no long term studies have been conducted.

The aim of this study was to establish whether the long term inhalation of HTS 6% decreased pulmonary exacerbations and the incidence of sputum colonisation and improved QOL and lung function.

Methods

Participants

Adults with bronchiectasis, confirmed by high resolution computed tomography, were recruited from the respiratory medicine department of a tertiary hospital in Melbourne, Australia.

Participants were eligible to be included if they were over 18 years old, were clinically stable, produced sputum daily and reported at least two exacerbations requiring antibiotics per year for the previous two years. They were excluded if they had CF, their FEV₁ decreased by more than 15% after the HTS challenge or their FEV₁ was less than 1 L at baseline. Ethical approval was granted by the Alfred Hospital Ethics Committee and written informed consent was obtained from all participants.

Study design

A prospective 12 month randomised controlled trial comparing IS with HTS 6% was conducted from January 2008 to October 2009. Assessors, therapists, participants and their physicians were blinded to treatment allocation. A co-investigator, who had no role in treatment allocation or outcome assessment, was un-blinded to manage adverse events. The study was registered with both the Clinical Trials Protocol Registration system (ACTRN12607000367448) and the Australian New Zealand Clinical Trials Registry (ACTRN12607000367448).

Measurement

At the screening visit spirometry was measured using standard protocols. Salbutamol (200 µg) was then administered via a metered dose inhaler and spacer and spirometry was repeated at least five minutes later. Hypertonic saline 6% (5 ml) was then inhaled via an AeronebGo mouthpiece micropump nebuliser (Niche Medical, Perth, Australia). Spirometry was repeated 20 minutes later. If the FEV₁ did not fall by ≥15%, participants were deemed safe to proceed with the trial.

Provided there were no signs or symptoms of a pulmonary exacerbation, participants returned two weeks later for their baseline visit. Spirometry was repeated and a sputum sample obtained for microbiology and culture. Exacerbations requiring antibiotics over the previous two years were recorded.

Two questionnaires, validated for non-CF bronchiectasis, were used to measure QOL: the St George’s Respiratory Questionnaire (SGRQ) and the Leicester Cough Questionnaire (LCQ). The minimal important difference (MID) for the SGRQ is four points for each domain and for the total score, with lower scores indicating better health-related QOL. The MID for the LCQ is 0.2 (physical), 0.2 (social), 0.8 (psychological) and 1.3 for the total score, with higher scores indicating better QOL. The number of people who achieved the MID for both QOL measures was calculated for each group.

Participants were then randomised (using a computer generated randomisation sequence concealed using sealed opaque envelopes) to receive either IS or HTS for the duration of the trial. The sachets of saline, distributed by the clinical trials pharmacy, were of the same size and appearance. Prior to commencing the inhalation of saline, participants were instructed to inhale two 100 µg puffs of salbutamol (Ventolin) via a Volumatic spacer (Allen & Hanburys). Whilst inhaling 5 ml of the saline solution via the nebuliser they were instructed to vary their inspiratory volume in cycles of larger and smaller breaths to optimise the deposition of the saline. This routine was repeated twice a day for 12 months and was documented in a home diary.

Participants were instructed to use only the nebulised saline for airways clearance. There were no restrictions on prescribed medications. The daily home diary recorded adherence, changes in medications and symptoms (a change in sputum volume or colour, new or increased haemoptysis, increased cough, dyspnoea, lethargy, a fever or increased sinus discharge). An exacerbation was defined as recording at least three symptoms in one day for two or more consecutive days. Exacerbations requiring commencement of antibiotics and exacerbations based on symptoms only, were calculated. At the end of each month, cough frequency was recorded using a visual analogue scale (VAS) with anchors of “never” and “continuously throughout the treatment”.

Home diaries were returned at
the three, six and 12 month visits and were analysed by an external assessor. The co-ordinator contacted the participants by telephone each week for the first month and then monthly for the remainder of the trial to reinforce the procedure and the completion of the home diary. Concerns regarding their treatment or their general health were directed to the un-blinded co-investigator.

Spirometry and QOL were repeated at three, six and 12 months when participants returned for review. Self reported hospital visits were recorded. At the 12 month visit, a sputum sample was obtained and participants and the treating physiotherapist were asked to nominate if they had been inhaling the “strong” or the “weak” salt solution, to assess the efficacy of blinding.

### Statistical analysis

Data were expressed as mean (SD) for normally distributed data or median and interquartile ranges (IQR) for data that were not normally distributed. Statistical analysis was performed for parametric data using a two way analysis of variance to account for group and time interaction (SPSS V.17.0; SPSS Inc). Post-hoc testing was conducted where a significant main effect was evident. Non-parametric data were compared between groups using the Mann Whitney U test. The significance level was set at $p < 0.05$.

For a 90% probability of detecting a difference in the number of exacerbations 30 subjects were required. This is based on the assumption that the true difference between groups is 0.5 exacerbations with a standard deviation of 0.4 exacerbations. For a 90% probability of detecting a difference between groups in FEV$_1$, 32 subjects were required. This is based on the assumption that the true difference between groups was 120 ml with a standard deviation of 100 ml. To account for an anticipated loss to follow-up of 25%, a total of 40 subjects were recruited.

### Results

Forty eight patients were screened (Fig. 1) with eight excluded prior to randomisation. Four declined inclusion and four did not meet the inclusion criteria: one due to a fall in FEV$_1$ following the HTS challenge and three due to screening FEV$_1$ values less than 1 L. Two participants from the HTS group withdrew at the three month assessment visit. One suffered from depression and was unable to adhere to the daily routine and the other declined further treatment. Both participants returned for all scheduled visits for measurement of outcomes and were included in the intention to treat analysis.

The baseline characteristics of the 40 randomised participants are shown in Table 1.

There was no significant difference between the two groups for any of the demographic variables at baseline or in the number of self reported exacerbations in the 12 months preceding the trial ($p = 0.86$). As expected, there was a 3:2 ratio of women to men in both groups and all of the participants had mild to moderate lung disease based on spirometry. There was only one protocol deviation
where one participant’s physician changed her bronchodilator from salbutamol to terbutaline.

There was no significant difference between groups for the number of exacerbations over the 12 months of the trial (Table 2). Nor was there a significant difference between groups for hospital admissions \((p = 0.34)\) or hospital days \((p = 0.36)\). Four participants had hospital admissions, three in the IS group for three, five and 61 days respectively and one in the HTS group for 68 days.

Quality of life significantly improved in both groups in all domains of both the SGRQ and the LCQ after three, six and 12 months (Tables 3 & 4). There were trends for more rapid improvement in the symptom and activity domains of the SGRQ in the HTS group over the first three months however no difference between groups was evident at 12 months for either the LCQ or the SGRQ (Figs. 2 & 3).

At baseline 60% of the participants in the IS group and 55% in the HTS group had a positive sputum culture for *Pseudomonas, Haemophilus, Aspergillus, Staphylococcus aureus* or *Streptococcus* with no significant difference in isolates between groups. At the completion of the trial there was a significant decrease in both groups with only 15% in each group having a positive sputum culture \((p = 0.046)\). There were no significant differences between groups in cough frequency reported by VAS at three \((p = 0.39)\), six \((p = 0.17)\) or 12 months \((p = 0.60)\).

There was no statistically or clinically significant difference in lung function between treatment groups at any time point (Table 5) however, significant improvements in FEV\(_1\) and FEF\(_{25-75}\%\) with respect to time were evident. Compared to baseline, FEV\(_1\) increased in both groups after six months (mean 90 ml; 11 to 169; \(p = 0.04\)), but this was not sustained at 12 months and there was no difference between groups (mean difference 0.06; 95% confidence interval –0.08 to 0.20; \(p = 0.39\)). FEF\(_{25-75}\%\) increased at all time points (mean 187 ml; 69 to 304; \(p = 0.001\)) in both groups with no difference between groups (0.04; –0.19 to 0.28; \(p = 0.71\)). There was no significant interaction between group allocation and time for FVC \((p = 0.67)\) but there was a trend towards a reduction in FVC in both groups at 12 months with no difference between groups (0.09; −0.07 to 0.25; \(p = 0.26\)).

There were three adverse events in the HTS group. One participant reported chest tightness during inhalation which resolved with treatment of an underlying acute exacerbation. Another reported an episode of hypertension which resolved without further intervention. This was judged by the patient’s physician to be unrelated to the intervention. Both participants continued in the trial without incident for the remainder of the 12 months. The third participant experienced an episode of rapid atrial fibrillation requiring attendance at the emergency department and subsequently elected to cease the saline inhalation prior to the three month assessment. There were no adverse events in the IS group.

Self reported adherence to therapy over 12 months was not significantly different between groups \((p = 0.86)\). The median number of inhalations missed over 12 months was 103 (IQR 25-226) in the IS group and 56 (IQR 22-311) in the HTS group. There was a significant decrease in adherence to therapy across all participants after six months (median 28 missed inhalations in the first six months versus 47 missed inhalations in the second six months \(p \leq 0.001\)). Fifty percent of participants correctly identified the treatment they had been receiving and the treating physiotherapist identified the correct therapy in 58% of the participants at the final visit. On completion of the trial 73% of participants chose to continue nebulised saline (IS, \(n = 6\), HTS, \(n = 23\)).

**Discussion**

This randomised controlled trial is the first long term study examining the effect of inhaled HTS 6% in non-CF

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**Table 2** Number of exacerbations over 12 months.

<table>
<thead>
<tr>
<th></th>
<th>IS (0.9%)</th>
<th>HTS (6%)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations</td>
<td>1.0 (0–4)</td>
<td>3.0 (0–6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Exacerbations requiring antibiotics</td>
<td>0.5 (0–3)</td>
<td>1.0 (0–2.5)</td>
<td>0.99</td>
</tr>
<tr>
<td>Exacerbation days</td>
<td>2.0 (0–26)</td>
<td>12.0 (1–26)</td>
<td>0.57</td>
</tr>
<tr>
<td>Exacerbation days requiring antibiotics</td>
<td>1.0 (0–19.5)</td>
<td>2.0 (0–7)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Data are median (IQR). IS: isotonic saline, HTS: hypertonic saline. \(p\) value for comparison of isotonic saline and hypertonic saline over 12 months.

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**Table 3** Impact on QOL – St George’s Respiratory Questionnaire.

|            | Baseline | 3 m | 6 m | 12 m | \(p\) value
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Symptom</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IS</td>
<td>64.1 (16.1)</td>
<td>57.0 (17.5) (\text{b})</td>
<td>51.2 (19.8) (\text{b})</td>
<td>50.7 (22.7) (\text{b})</td>
<td>0.18</td>
</tr>
<tr>
<td>HTS</td>
<td>64.3 (14.2)</td>
<td>48.5 (21.0) (\text{b})</td>
<td>57.6 (20.0) (\text{b})</td>
<td>52.3 (22.9) (\text{b})</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IS</td>
<td>39.4 (22.2)</td>
<td>35.4 (22.4) (\text{b})</td>
<td>31.0 (21.3) (\text{b})</td>
<td>34.7 (25.1) (\text{b})</td>
<td>0.18</td>
</tr>
<tr>
<td>HTS</td>
<td>50.1 (24.4)</td>
<td>39.8 (28.5) (\text{b})</td>
<td>33.6 (25.2) (\text{b})</td>
<td>37.4 (25.9) (\text{b})</td>
<td></td>
</tr>
<tr>
<td>Impact</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IS</td>
<td>33.5 (17)</td>
<td>27.2 (17.9) (\text{b})</td>
<td>22.8 (15.2) (\text{b})</td>
<td>23.3 (19.1) (\text{b})</td>
<td>0.60</td>
</tr>
<tr>
<td>HTS</td>
<td>35.6 (16.9)</td>
<td>26.8 (19.6) (\text{b})</td>
<td>22.0 (13.5) (\text{b})</td>
<td>27.7 (19.3) (\text{b})</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean (standard deviation). IS: isotonic saline, HTS: hypertonic saline, \(m\): months.

\(p\) value for group \(\times\) time interaction.

\(p < 0.05\) compared to baseline.
bronchiectasis. Treatment over 12 months was well tolerated and resulted in similar clinically important benefits with significant improvements seen in QOL, lung function, and sputum colonisation in both groups when inhaling either IS or HTS. There was no difference between groups in exacerbation rates.

This study did not identify any clinically important superiority of inhaled HTS over IS in non-CF bronchiectasis. This is perhaps contrary to a previous finding where HTS was found to be more effective than IS in decreasing sputum viscosity and increasing sputum yield during four single treatments in patients with non-CF bronchiectasis who produced less than 10 mg of sputum each day. The differences in results may be explained by the extended length of our treatment or the different outcomes measured in the two trials. Hypertonic saline 7% inhalation has also been found to be superior to IS in patients with CF, with significant improvements in QOL and lung function and a significant decrease in exacerbations. Our finding of no difference between groups may be due to the smaller sample size or to the electrolyte content and rheology of CF sputum which differ from that of non-CF sputum. This confirms previous observations that treatments beneficial for CF may not have the same effects in non-CF bronchiectasis.

It is possible that HTS may have anti-inflammatory as well as rheological effects on airway mucus in CF bronchiectasis by clearance of IL-8 and protease activity such as neutrophil elastase. Further studies are required to ascertain if sub-groups of disease severity and aetiology are more likely to respond to varied or higher sodium chloride concentrations. It is interesting to note that nearly three quarters of the participants chose to continue nebulised saline suggesting that overall acceptance and perception of benefits was high.

Clinically relevant benefits were evident in both treatment groups over 12 months. The presence of organisms such as *Pseudomonas aeruginosa*, *Haemophilus influenzae* and *Staphylococcus aureus* are associated with reduced QOL. The significant decrease in the presence of these organisms following the use of IS or HTS may be attributable to the improved hydration of the airway, resulting in enhanced airways clearance. It is important to note that prior to commencement on the trial 85% of the participants were regularly using airways clearance techniques.

![Figure 2](image_url) **Figure 2** SGRQ Totals. No significant difference between groups at any time point.

![Figure 3](image_url) **Figure 3** LCQ Totals. No significant difference between groups at any time point.

### Table 4 Impact on QOL — Leicester Cough Questionnaire.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 m</th>
<th>6 m</th>
<th>12 m</th>
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<tbody>
<tr>
<td><strong>Physical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IS</td>
<td>4.2 (1.7)</td>
<td>4.9 (1.0)</td>
<td>5.1 (1.4)</td>
<td>5.3 (1.3)</td>
</tr>
<tr>
<td>HTS</td>
<td>4.4 (1.0)</td>
<td>5.3 (1.0)</td>
<td>5.0 (1.1)</td>
<td>5.1 (1.1)</td>
</tr>
<tr>
<td><strong>Psychological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IS</td>
<td>3.9 (1.5)</td>
<td>5.0 (1.4)</td>
<td>5.4 (1.4)</td>
<td>5.5 (1.6)</td>
</tr>
<tr>
<td>HTS</td>
<td>4.7 (1.3)</td>
<td>5.9 (1.1)</td>
<td>5.3 (1.0)</td>
<td>5.7 (1.0)</td>
</tr>
<tr>
<td><strong>Social</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IS</td>
<td>4.4 (1.4)</td>
<td>5.2 (1.3)</td>
<td>5.6 (1.3)</td>
<td>5.7 (1.4)</td>
</tr>
<tr>
<td>HTS</td>
<td>4.6 (1.2)</td>
<td>5.7 (1.4)</td>
<td>5.5 (1.0)</td>
<td>5.6 (1.0)</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation). IS: isotonic saline, HTS: hypertonic saline, m: months.

$^a$ p value for group × time interaction.

$^b$ p < 0.05 compared to baseline.
The improvements in lung function, compared to baseline, are likely to be clinically relevant as they go against the expected trend of gradual decline in this cohort of patients. However, the decrease in lung function and QOL between the six and 12 month visits is likely to reflect the significant decrease in adherence to therapy in both groups over this period and suggests that, for this treatment to be effective, it needs to be undertaken on a regular basis.

The improvements seen in both groups may have been due to the inhalation of the saline solution or alternatively could be due to pre-medication with Salbutamol. It is unlikely however that this would be the case. A short term four arm study showed an increased sputum yield in both the IS and HTS groups compared to Terbutaline alone, suggesting that Salbutamol was unlikely to have contributed markedly to the improvement seen in both groups.

The analysis of exacerbations is complicated by the lack of a standardised definition of an exacerbation in this population of patients and the relatively small sample size may have masked any differences between groups in exacerbation rates. In non-CF bronchiectasis the improvement in QOL is one of the most important outcome measures. An association between more frequent exacerbations and lower QOL has previously been demonstrated in non-CF bronchiectasis and given the significant improvements in QOL demonstrated here, it is possible that there was an associated reduction in exacerbation rate in both groups compared to the previous year. A 12 month run-in period recording exacerbations would have been ideal to ascertain if this was the case and should be investigated in larger studies. The small number of hospital admissions may possibly be attributed to increased clinical management as a result of participating in the trial.

A possible limitation of the trial was that the taste of the saline solutions was not masked by the addition of quinine (previously used as a blinding agent). As participants were naïve to nebulised saline, were not informed of the salt concentration of the challenge test and packaging of the two solutions was identical, we are confident that participants remained blinded. In a recent study involving the inhalation of IS (where a salty taste is not expected), 17% of patients reported a salty taste. Importantly, at trial completion, only 50% of the participants correctly identified their treatment allocation so the taste of the solution was unlikely to have biased the study.

Acknowledgements

We were greatly appreciative of NicheMedical’s donation of the AeronebGo nebulisers and Allen & Hanbury’s provision of Volumatic spacers. The authors would also like to acknowledge Mrs Rachel Gourlay for her assistance with data management and Dr Annemarie Lee for technical and manuscript assistance.

Funding

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Ethics approval

This study was conducted with the approval of the Alfred Hospital Ethics Committee.

<table>
<thead>
<tr>
<th>Table 5 Lung function.</th>
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<tr>
<td></td>
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<tr>
<td>FEV₁</td>
</tr>
<tr>
<td>IS</td>
</tr>
<tr>
<td>HTS</td>
</tr>
<tr>
<td>FVC</td>
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<tr>
<td>IS</td>
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<td>HTS</td>
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<tr>
<td>FEF₂₅⁻⁷⁵%</td>
</tr>
<tr>
<td>IS</td>
</tr>
<tr>
<td>HTS</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation). FEV₁: forced expiratory volume in 1 s, FVC: forced vital capacity, FEF₂₅⁻⁷⁵%: forced expiratory flow at 25–75% of the forced vital capacity, IS: isotonic saline, HTS: hypertonic saline. p value for group × time interaction.
Conflict of interest statement

Niche Medical provided the AeronebGo nebulisers and Allen & Hanbury provided the Volumatic spacers but neither were involved in the study design, collection or interpretation of data, or preparation of the manuscript. None of the co-authors had any conflicts of interest.

References