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Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis

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Summary Sputum clearance is of prime importance in the management of patients with bronchiectasis. While nebulised normal isotonic saline (0.9%) (IS) has been anecdotally used to treat patients with tenacious sputum, the use of hypertonic saline (7%) (HS) could have potential muco-protective and clearance properties.

24 patients with bronchiectasis were randomised to receive four single treatment schedules in random order: (1) active cycle breathing technique (ACBT) alone, (2) nebulised terbutaline then ACBT, (3) nebulised terbutaline, nebulised IS then ACBT and (4) nebulised terbutaline, nebulised HS then ACBT.

Sputum weights were significantly higher after HS than IS ($P = 0.002$). Ease of expectoration also differed overall ($P = <0.0001$) and was significantly lower with HS than with IS ($P = 0.0005$). Sputum viscosity differed between treatment phases, with a significant linear trend to reduced sputum viscosity with HS ($P = 0.0002$). These changes were associated with small but statistically significant differences in FEV_1 ($P = 0.043$) and FVC ($P = 0.011$) between treatment phases.

Nebulised hypertonic saline can be used safely and effectively as an adjunct to physiotherapy in selected patients. A long-term prospective trial is now indicated to determine its effectiveness on long-term infection rate, quality of life and lung function.

Introduction

For patients with bronchiectasis sputum retention is a distressing symptom and arguably the most important factor in maintaining the vicious cycle of respiratory infection, inflammation and further sputum production. The use of nebulised ''normal'' 0.9% isotonic saline (IS), as a method of enhancing mucociliary clearance has become a clinically accepted adjunct to physiotherapy in the treatment of many chronic lung conditions but it has little scientific evidence on which to base its use. 7% hypertonic saline (HS) is being increasingly used in clinical practice,[1] specifically for diagnostic purposes in other lung conditions, but its use as a mucolytic agent is poorly understood as there are few published human studies which evaluate its role in reducing sputum viscosity. The sodium and chloride concentrations in sputum produced in bronchiectasis are below those found in plasma (hypotonic), and also below the optimum for ciliary transportability of sputum.[2] Administration of a

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hypertonic sodium chloride solution may increase mucociliary clearance by influencing ciliary function, increasing the osmotic drive, altering the visco-elasticity of sputum, and, therefore, reducing the viscosity and aiding sputum clearance.

Sputum volumes in bronchiectasis patients vary between 20 and 500 mls per day but previous physiotherapy studies have excluded patients who produce less than 30 g per day.[3] The aim of this study was to evaluate nebulised 7% HS as an adjunct to physiotherapy airway clearance techniques in patients with stable bronchiectasis who produce less than 10 g of sputum per day, and to compare this with nebulised 0.9% IS and airway clearance alone. Advances in diagnostic techniques (high resolution CT scanning) allow patients to be diagnosed much earlier in the disease process, and we therefore see patients with minimal sputum despite recurrent infections, despite having radiologically established disease. This theoretically allows the opportunity to institute treatment earlier and the best chance of limiting disease progression.

Methodology

Twenty-four consecutive patients, 17 females, (55 ± 3.6 yrs) and 7 males (64 ± 3.8 yrs) with stable newly diagnosed bronchiectasis, diagnosed by high resolution CT scanning, who had not previously had physiotherapy input were referred from chest physicians to take part in the study. All of the patients reported difficulty in expectorating 'thick, sticky' sputum and had required at least one course of antibiotics in the last 6 months (mean 1.8). Prior to approaching the patients, consent for inclusion was obtained from the patients by respective chest physicians. Once consultant consent was obtained patients were given a full written and verbal explanation of the study. Written informed consent was then obtained prior to the HS challenge test. Ethical approval was obtained from the local research ethics committee.

Allergic broncho-pulmonary aspergillosis and cystic fibrosis phenotypes were excluded. Patients were able to continue all routine medication (inhaled/nebulised bronchodilators, long acting bronchodilators, leukotriene antagonists, oral or inhaled steroids) but were excluded if they had been prescribed a course of antibiotics in the last month or required antibiotics during the course of the study.

To establish average daily sputum production patients collected all daily expectorated sputum for 7 days. This was all weighed 'wet' to determine sputum production of less than 10 g. Non-isotonic solutions may cause bronchospasm and subsequent reduction in lung function. Prior to commencing the study patients underwent a nebulised HS challenge test and were to be excluded from the study if they reported 'chest tightness', 'wheeze' or 'difficulty in breathing', or had a 10% reduction in spirometry following inhalation of HS. In fact there were no patients excluded following the challenge test. One male patient failed to attend for follow up, and was therefore excluded, but complete data was available for the remaining 23 patients.

A cross-over study design was used with computer determined random allocation to four single session treatment schedules. The patients attended once weekly over a four week period to complete all treatment schedules. Nebulised terbutaline was used in phases (2, 3, 4) as a premedication to minimize adverse effects.

Treatment schedules

(1) Active cycle breathing technique (ACBT) alone.
(2) Nebulised terbutaline followed by ACBT after 10 min.
(3) Nebulised terbutaline followed after 10 min by nebulised isotonic saline (0.9%) then ACBT.
(4) Nebulised terbutaline followed after 10 min by nebulised hypertonic (7%) then ACBT.

IS and HS solutions were produced by the pharmacy in blinded labeled sterile solutions. The physiotherapist performing challenges and sputum assessments remained blinded to IS and HS throughout the study. Nebulisation of all solutions was carried out in a supported upright position, breathing at normal tidal volume and respiratory rate for 5 min.[4] Patients performed ACBT immediately following nebulisation of both IS and HS as time to maximum effect is not known. The ACBT, as described by Pryor and Webber,[5] was performed in right and left side lying positions, as some patients were unable to tolerate standard postural drainage positions. It is recommended that treatment time is adapted for each patient.[6] For patients with a moderate amount of sputum a minimum of 10 min in any one position is usually necessary. As treatment was carried out in 2 positions a minimum treatment duration of 10 min and a maximum of 20 min (mean 16 min) was set for all patients. The end point of treatment was standardized to be when an effective huff to low lung volume in 2 consecutive cycles was dry sounding and unproductive. The four periods of treatment administration

were separated by a 'wash out' period of 1 week to enable the patients condition to return to a level uninfluenced as far as possible by the treatment previously received.

Outcome measures used in the study were; wet sputum weight (grams), sputum viscosity (no sputum production and pourability grades 1–4), ease of expectoration visual analogue scale (VAS) and spirometry (FEV_1, FVC). All expectorated sputum was weighed wet immediately following each treatment phase. This was done using pre-calibrated electronic scales. Measuring wet sputum weight has been shown to be a reliable and valid method of assessing sputum expectorated during ACBT.[7] The facilities were not available to measure sputum viscosity using a rheometer and therefore a viscosity pourability grading was used. A highly significant correlation has been shown between this pourability grade and sputum viscosity measured using a rheometer.[8] Spirometry was performed in each treatment schedule 1 pre and post ACBT, 2 pre nebulised terbutaline, post nebulised terbutaline and post ACBT, 3 pre nebulised terbutaline, post terbutaline, post IS and post ACBT and in schedule 4 pre nebulised terbutaline, post terbutaline, post HS, and post ACBT.

Non-parametric analysis was used as the data was not normally distributed and a significance level of $P<0.05$ was used throughout. The Friedman test assessed general, non-specified differences across the interventions and between individual treatments in each intervention group.

Results

There were significant differences in sputum weight (Freidman T2 = 36.15, $P<0.0001$) and ease of expectoration visual analogue scores (Freidman T2 = 31.14, $P<0.0001$) and small but significant differences in lung function tests (Table 1). Post hoc multiple comparisons using contrasts suggested significant differences between all comparison groups except the bricanyl and IS groups.

Further analysis (by Wilcoxon, Chi^2 and Mann–Whitney tests) then revealed real differences between all the intervention groups but the findings from the IS and HS groups were of primary interest. All but two patients produced more sputum when treated with HS compared to IS ($z = -0.377$, $P = 0.0002$) and although differences were found between each intervention for ease of expectoration, the lowest scores were recorded following HS.

Sputum viscosity was analysed by comparing the frequency of grades occurring in each of the 4 intervention groups. There was a significant overall difference in the distribution of sputum viscosity grades between the different treatment phases ($Chi^2 = 34.62$ (12df), $P = 0.0005$). Combination of the categories of no sputum with grades 1 and 2, and grades 3 with 4, confirmed this difference (Total $Chi^2 = 18.18$ (3df), $P = 0.0004$) and showed a significant trend to higher grade of sputum viscosity from ACBT through bricanyl, IS and HS treatment phases (Chi^2 for linear trend = 13.46 (1df), $P = 0.0002$) (Table 2).

Eight patients had the same sputum viscosity grade with IS and HS. However, 12 patients increased by 1 grade and 3 patients by 2 grades; no patients had a reduced grade. McNemars test demonstrated that sputum grade was significantly more likely to increase to grade 3 or 4 with HS than with IS (Yates Corrected $Chi^2 = 7.11$ (1df), $P = 0.008$). These changes were associated with small differences in FEV_1 ($P = 0.043$) and FVC ($P = 0.011$) between treatment phases, however, there were no significant difference in FEV_1 ($P = 0.12$) or FVC ($P = 0.23$) between IS and HS treatments.

There was a significant difference in ease of expectoration visual analogue scores between the different treatment phases. Multiple comparisons suggested significant differences between each treatment phase, with lowest scores following HS

Table 1 Summary results of sputum weight, ease of expectoration and spirometry in each treatment phase.

	Sputum wt (g) Median (IQR)	VAS (0–10) Median (IQR)	FEV_1 (l) Median (IQR)	FVC (l) Median (IQR)
ACBT alone	1.40 (0.88–3.30)	8.00 (6.18–9.40)	1.70 (1.21–2.19)	2.30 (1.58–2.70)
Terbutaline alone	2.75 (1.35–4.58)	7.70 (4.43–8.98)	1.80 (1.20–2.35)	2.60 (1.76–2.98)
IS (0.9%)	3.17 (1.45–6.25)	5.20 (2.75–8.38)	1.85 (1.36–2.20)	2.55 (1.91–2.94)
HS (7%)	5.3 (2.97–9.33)	2.40 (1.43–5.40)	2.00 (1.25–2.40)	2.50 (1.79–3.08)
Friedman Test	T2 = 36.15 $P<0.0001$	T2 = 31.14 $P<0.0001$	T2 = 2.87 $P = 0.043$	T2 = 4.03 $P = 0.011$

Table 2 Chi^2 comparison of sputum viscosity.

	No sputum + Grades 1 and 2	Grades 3 and 4
ACBT	20	3
Terbutaline	20	3
IS	18	5
HS	9	14

Total $Chi^2 = 18.18$ (3df), $P = 0.0004$.
Chi^2 for linear trend = 13.46 (1df), $P = 0.0002$.
(Combined groups of (no sputum, grades 1 and 2) and (grades 3 and 4) in each treatment phase).

followed by IS, bricanyl and finally ACBT alone (Friedman test T2 = 31.14, $P < 0.0001$).

Discussion

Following the initial insult that causes bronchiectatic change, progression of disease is intimately related to sputum retention, leading to a vicious cycle of infection, inflammation and further sputum production. Expectoration of sputum is, therefore, vitally important to limit disease progression. This study has shown that in this selective group of patients producing less than 10 g per day, an acute beneficial treatment effect can be demonstrated. Both nebulised IS and HS were significantly more effective in increasing sputum yield, reducing sputum viscosity and improving ease of sputum expectoration when compared to ACBT alone. However, HS was significantly better than IS, for sputum weight, viscosity and ease of expectoration.

Bricanyl, IS and HS significantly increased treatment phase and total sputum weight compared to ACBT alone. Direct application of bricanyl is known to increase ciliary beat frequency, tracheal mucus velocity, and whole lung clearance of airway secretions Furthermore, $Beta_2$ sympathomimetics have been shown to stimulate ion transport and water shift towards the airway lumen, possibly increasing hydration. Thus the enhanced sputum yield after the nebulisation of bricanyl may be due to direct hydration or specific B_2 adrenergic stimulation or both mechanisms. The bronchodilation that follows bricanyl may also aid the effectiveness of physiotherapy, perhaps by increasing effective expiratory flow rates or improving regional ventilation. However, comparison of the two primary intervention groups (IS and HS) showed that in all but two patients sputum weight increased when treated with HS compared to IS. The improvements in mucociliary clearance seen following administration of HS may therefore result from increases in the salinity of the retained secretions, in particular, the gel surface where improved interactions with cilia may result in increased ciliary clearance.

Sputum viscosity significantly differed between groups and was lowest in the HS phase. Clinically this finding may be of great importance, as a reduction in sputum viscosity will enhance the effectiveness of sputum clearance. As a result patients may find that chest clearance requires less effort and is less tiring.

The reduction in sputum viscosity seen in this study following HS support previous work suggesting that sputum is saline dependent, and that the nebulisation of HS has a direct effect on sputum composition and visco-elasticity.[2] The HS may have achieved its effect by promoting hydration of airway secretions in response to the osmotic gradient created after the inhalation of HS.[9] It may also cause changes in ionic concentrations, resulting in conformational changes that alter rheologic properties of sputum and allow more effective sputum clearance.[10] These effects on viscoelasticity are thought to be more likely explanations rather than increases in ciliary activity.[11] However the absolute mechanism responsible for the observed benefits needs to be elucidated with more certainty.

Increased sputum weight and reduced viscosity were accompanied by an increased ease of expectoration. A significant difference was found between each treatment phase, with the lowest scores following HS. This implies that despite producing more sputum patients find it easier to expectorate, probably due to reduced viscosity. Clinically this finding is important as if patients find the sputum easier to expectorate; performing ACBT will be easier, more effective and less tiring. This may result in improved compliance.

Although only a secondary endpoint, spirometry parameters were also measured. Because of the small numbers comparison of HS and IS did not demonstrate a significant difference, but overall a trend for improving FEV_1 from ACBT alone to treatment produced a statistically significant and arguably clinically significant improvement.

There have been no previous published reports of the clinical effects of HS with bronchiectasis patients but this study has shown that in stable patients with low sputum yield, 7% HS is a well tolerated, safe and easily administered adjunct to physiotherapy airway clearance techniques and is more effective than 0.9% IS. To allow application to other patients with bronchiectasis the study needs

to be repeated in patients with different disease severity's who produce sputum volumes >10 g per day. A prospective long-term study is now indicated to determine its effectiveness on long-term infection rate, quality of life and lung function.

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