Adults with cystic fibrosis prefer hypertonic saline before or during airway clearance techniques: a randomised crossover trial

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Question: Among adults with cystic fibrosis, does the timing of hypertonic saline relative to airway clearance techniques affect lung function, perceived efficacy, tolerability, or satisfaction with the entire airway clearance regimen, and is the preferred timing regimen stable over time? Design: A randomised crossover trial with concealed allocation, intention-to-treat analysis, and blinded assessors. Participants: 50 adults with cystic fibrosis and stable lung function at the end of a hospital admission. Intervention: Participants performed 3 sessions of airway clearance techniques per day for 3 days. On each day, participants were randomised to inhale hypertonic saline either before, during, or after the airway clearance techniques. Participants readmitted within one year repeated the 3-day study. Outcome measures: The primary outcome was the change in forced expiratory volume in one second (FEV₁) from before to 2 hours after an entire airway clearance session. Secondary outcomes were change in forced vital capacity, perceived efficacy, tolerability, satisfaction, adverse events, and adherence. Results: All 50 participants completed the study. The effects on lung function were non-significant or were of borderline statistical significance favouring inhalation of hypertonic saline before airway clearance techniques. Satisfaction was rated significantly worse on a 100 mm scale when hypertonic saline was inhaled after the airway clearance techniques: mean differences 20mm (95% CI 12 to 29) compared to before the airway clearance techniques and 15 mm (95% CI 6 to 24) compared to during the techniques. Perceived effectiveness showed similar effects but other outcomes were unaffected. All 14 participants who were readmitted repeated the study and most preferred the same timing regimen. Conclusion: People with cystic fibrosis could be encouraged to time hypertonic saline before or during airway clearance techniques to maximise perceived efficacy and satisfaction, even though lung function may not be better with these timing regimens. Trial registration: ACTRN12611000673943. [Dentice RL, Elkins MR, Bye PTP (2012) Adults with cystic fibrosis prefer hypertonic saline before or during airway clearance techniques: a randomised crossover trial. Journal of Physiotherapy 58: 33–40]

Key words: Cystic fibrosis, Hypertonic saline, Airway clearance techniques, Lung function, Physiotherapy

Introduction

Cystic fibrosis is the most common life-shortening genetic disease in Caucasians. In Australia, 3200 people have cystic fibrosis, of whom half are adults (Bell et al 2011). People with cystic fibrosis have dehydration of the airway surface, which impairs the clearance of normal airway secretions by cough and mucociliary clearance (Boucher 2007). This causes chronic lung infection with recurrent exacerbations, progressive lung damage, and eventual respiratory failure.

Airway clearance techniques, inhaled medications, and exercise are frequently used to promote mucus clearance in an attempt to slow the progression of infection and lung damage (Bye and Elkins 2007, Dwyer et al 2011, Kuys et al 2011, Pryor and Prasad 2008). Physiotherapists may apply manual techniques, such as percussion and vibration, or teach independent techniques, such as breathing through a positive expiratory pressure device (Elkins et al 2006a, Main et al 2009, van der Schans et al 2005). These techniques are believed to promote mucus clearance by accelerating expiratory airflow, reducing airway obstruction or closure, and improving the rheology of mucus (App et al 1998, Dasgupta et al 1998, Dasgupta et al 1995). Nebulised hypertonic saline is one inhaled medication that accelerates mucus clearance, by hydrating the airways, improving the rheology of the mucus, and stimulating cough (Donaldson et al 2006, King et al 1997, Robinson et al 1997, Robinson et al 1996, Wills et al 1997). Restoration of airway hydration peaks immediately after an inhalation, increasing mucus clearance for minutes and possibly hours (Donaldson et al 2006, Goralski et al 2010). Hypertonic saline may also directly affect the most common infective organism in the cystic fibrosis lung, Pseudomonas aeruginosa, by promoting less virulent strains and disrupting its protective biofilm (Behrends et al 2010, Williams et al 2010). Hypertonic saline can cause transient airway narrowing, coughing, and pharyngeal discomfort, but these symptoms become less severe with regular use such that only about 8% of people with cystic fibrosis find hypertonic saline intolerable (Elkins and Bye 2006).

Airway clearance techniques and hypertonic saline are often used in a single treatment session. In clinical trials examining the efficacy of hypertonic saline, each dose has been inhaled immediately before airway clearance techniques.
(Wark and McDonald 2009). However, hypertonic saline could also be inhaled during or after airway clearance techniques. The timing of these two interventions could potentially impact the efficacy, tolerability, convenience, and duration of the overall airway clearance regimen. Nebulisation of hypertonic saline before airway clearance techniques is often recommended to ensure the airway is hydrated and mucus rheology is improved before the techniques are commenced. Nebulisation during airway clearance techniques could save time and may capitalise on the immediate peak in the airway surface liquid volume. However, it could increase the complexity of the overall airway clearance session. Nebulisation after airway clearance techniques may capitalise on the reduction in airway obstruction by mucus and therefore allow delivery of the hypertonic saline to a greater proportion of the bronchial tree. However, delivering the hypertonic saline more directly to the airway epithelium, rather than to overlying mucus, may reduce tolerability.

The effect of the timing of hypertonic saline in relation to airway clearance techniques is yet to be investigated in a controlled setting (Elkins and Dentice 2010). Furthermore, it is not known whether a person's preferred order of administration of these two interventions remains stable over time. Therefore, the research questions were:

1. Among adults with cystic fibrosis, does the timing of hypertonic saline relative to airway clearance techniques change the effect of an entire airway clearance session on lung function?
2. Does the timing of hypertonic saline affect the perceived efficacy, tolerability, or satisfaction with the entire airway clearance regimen?
3. Do adults with cystic fibrosis change their preferred timing regimen over time?

**Method**

**Design**

A randomised, crossover trial with concealed allocation, blinding of assessors, and intention-to-treat analysis was undertaken at Royal Prince Alfred Hospital, Sydney. Participants were recruited from among inpatients of the Cystic Fibrosis Unit, towards the end of a hospital admission when improvements in clinical status had stabilised and a daily therapy routine was well established. One investigator checked that each participant was performing appropriate airway clearance techniques and tolerating hypertonic saline three times daily. On the first study day, participants were randomly allocated to perform hypertonic saline either before, during, or after airway clearance techniques at all airway clearance sessions that day. On the next day, participants used the next randomly allocated timing regimen at all airway clearance sessions. On the third day, participants used the remaining timing regimen at all airway clearance sessions. Randomisation was computer generated and balanced the number of participants who experienced the three timing regimens in each of the six possible orders. Concealment of the allocations was achieved using sealed opaque envelopes. After the 3-day study was complete, participants were followed for one year to observe whether they had another hospital admission. Those who had a second hospital admission were invited to repeat the 3-day study to determine whether their preferred timing regimen had changed.

**Participants**

Patients were required to meet the following criteria to be eligible for the study: aged at least 18 years, a diagnosis of cystic fibrosis confirmed with sweat testing or genotyping, able to perform airway clearance techniques and hypertonic saline inhalation on a regular basis, and clinically stable with a forced expiratory volume in one second (FEV1) within 10% of the best recorded value for the past 6 months. Patients were excluded from the study if they met any of the following criteria: naïve to hypertonic saline, intolerant of hypertonic saline, lung transplant recipient, colonised with *Burkholderia cepacia* complex, not clinically stable, haemoptysis greater than 60 mL within the last month, thrombocytopenia, or pregnancy. Participants who were readmitted to hospital within one year were required to meet the same eligibility criteria before they were invited to repeat the 3-day study.

**Intervention**

**Inhalation solution:** The hypertonic saline solution used in the study was 6% hypertonic saline. Participants were instructed to inhale 4 mL of the hypertonic saline solution at each of three sessions of airway clearance techniques for that day. A Pari LC plus nebuliser was given to all participants to administer their hypertonic saline. Participants who were regularly using a bronchodilator at enrolment were advised to use their current bronchodilator before every dose. Participants who did not usually use a bronchodilator inhaled 200 micrograms of salbutamol sulphate via a metered dose inhaler and a spacer device prior to each dose of hypertonic saline.

**Airway clearance techniques:** During the hospital admission and prior to enrolment into the study, a daily routine of airway clearance techniques and hypertonic saline was established by an experienced respiratory physiotherapist. The techniques were chosen for each participant according to perceived efficacy and participant preference, and aligned with the recommended application of the selected techniques (McIlwaine and Van Ginderdeuren 2009). Subjects performed this airway clearance regimen for each session with or without an assistant as required. The duration and type of airway clearance techniques were established in the days prior to randomisation and were maintained across the three study days.

**Timing regimens:** When participants were allocated to inhale hypertonic saline before or after airway clearance techniques, they were advised to commence the second intervention as soon as the first intervention was complete. When participants were allocated to inhale hypertonic saline during airway clearance techniques, participants and the treating therapist decided collaboratively if this would be performed by simultaneous administration or by alternating short periods of inhalation and techniques, eg, 10–15 breaths of hypertonic saline followed by airway clearance techniques, performed in cycles until the treatment session was completed. However, participants using mouthpiece positive expiratory pressure as their airway clearance technique were not permitted to administer hypertonic saline simultaneously as this alters the inhaled dose and the distribution of its deposition (Laube et al 2005). Alternating administration of these two interventions was always used instead.
Participants received other usual care on all three study days, including all other routine therapies. Other inhaled therapies (eg, dornase alpha, corticosteroids) were administered at a consistent time of day that was more than one hour from any of the three study periods. Typically, dornase alpha was inhaled in the morning or evening, according to patient preference (Bishop et al 2011, Dentice and Elkins 2011).

**Outcome measures**

Lung function was measured using a standard spirometer* according to American Thoracic Society guidelines (American Thoracic Society 1995). The spirometric measures recorded were FEV₁ and forced vital capacity (FVC), with each calculated in litres and as a percentage of the predicted value (Knudson et al 1983). The spirometric measures were recorded prior to the second treatment session each day. Participants then had a bronchodilator, and then inhaled hypertonic saline either before, during, or after airway clearance techniques, as allocated for that day. The spirometric measures were recorded again 2 hr after the baseline measurement, and the change in FEV₁ and FVC over this 2-hr period for each of the study days was calculated. The physiotherapist who recorded the spirometric measures was kept unaware of the timing regimens allocated to all participants.

The perceived effectiveness, tolerability, and satisfaction with each timing regimen were reported by participants at the end of the day after all treatments using that regimen had been experienced. Effectiveness was rated on a 100 mm visual analogue scale with the descriptors ‘poor’ at 0 mm and ‘excellent’ at 100 mm. Tolerability and satisfaction were also measured the same way.

Adverse events (such as haemoptysis, pharyngitis, and excessive coughing) were recorded after each treatment session. Whether an adverse event was severe enough to lead to intolerance of the trial intervention was also recorded. A blinded investigator questioned participants specifically regarding these events.

Adherence was assessed by counting unused sachets of hypertonic saline, and through documentation of each session of airway clearance techniques and hypertonic saline in the participant’s hospital case records. Furthermore, a physiotherapist attended each airway clearance session, even if the airway clearance techniques were to be performed independently, to confirm compliance with the allocated timing regimen.

At the conclusion of the 3-day study, participants reported their preferred timing regimen.

For participants who repeated the 3-day study during the year of follow-up to determine if their preferred timing regimen had changed, perceived effectiveness, tolerability, satisfaction, preferred timing regimen, adherence, and adverse events were measured as previously.

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*spirometer
FEV1 was chosen as the primary outcome because it has the potential to reflect both treatment efficacy and airway narrowing. We were unable to find an estimate of the smallest effect on FEV1 that adults with cystic fibrosis would consider makes using a particular timing regimen worthwhile. However, given that the timing regimens typically require similar time, effort, and expense, we postulated that even a very small effect would be worthwhile. Therefore we sought a difference of 150 mL between groups for the change in FEV1 across an individual treatment session. Pilot data provided a SD of 173 mL for this change in FEV1 among four adults with cystic fibrosis who met the eligibility criteria. Assuming this SD, 13 participants would provide 80% power, at the 2-sided 5% significance level, to detect a 150 mL difference in FEV1 as statistically significant between two groups in the study. We increased this to 32 to allow for multiple between-group comparisons and some loss to follow-up.

We also sought to have sufficient statistical power to identify the smallest effect on satisfaction that would make it worthwhile to use one timing regimen instead of another. Again, given no established value and given that the timing regimens require similar time, effort, and expense, we nominated 10 mm on the 100 mm visual analogue scale as the threshold. Assuming a SD of 20 mm (Dentice et al 2006), 34 participants would provide 80% power, at the 2-sided 5% significance level, to detect a 10 mm difference in satisfaction between two groups. We increased this to 50 to allow for multiple between-group comparisons and some loss to follow-up.

### Table 1. Baseline characteristics of participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Randomised participants</th>
<th>Initial 3-day study (n = 50)</th>
<th>Repeat 3-day study (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td>31 (10)</td>
<td>30 (8)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td>46 (56)</td>
<td>43 (64)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td>21 (12)</td>
<td>21 (14)</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td></td>
<td>1.93 (0.78)</td>
<td>1.59 (0.66)</td>
</tr>
<tr>
<td>FEV1 (% pred)</td>
<td></td>
<td>57 (22)</td>
<td>45 (14)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td></td>
<td>3.29 (1.03)</td>
<td>3.04 (1.02)</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td></td>
<td>80 (20)</td>
<td>71 (14)</td>
</tr>
<tr>
<td>Enrolment (day of hospital stay), mean (SD)</td>
<td></td>
<td>9 (2)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Outpatient bronchodilator use, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nil</td>
<td>12 (24)</td>
<td>6 (12)</td>
<td></td>
</tr>
<tr>
<td>occasional</td>
<td>3 (6)</td>
<td>2 (14)</td>
<td></td>
</tr>
<tr>
<td>regular</td>
<td>30 (60)</td>
<td>9 (64)</td>
<td></td>
</tr>
<tr>
<td>Outpatient hypertonic saline use, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nil</td>
<td>23 (46)</td>
<td>6 (12)</td>
<td></td>
</tr>
<tr>
<td>occasional</td>
<td>15 (30)</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>regular</td>
<td>12 (24)</td>
<td>9 (64)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Mean (SD) of groups, mean (SD) difference within groups, and mean (95% CI) difference between groups for lung function.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Groups</th>
<th>Difference within groups</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hr</td>
<td>2 hr minus 0 hr</td>
<td>2 hr minus 0 hr</td>
</tr>
<tr>
<td></td>
<td>Before (n = 32)</td>
<td>During (n = 32)</td>
<td>After (n = 32)</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>1.94 (0.89)</td>
<td>1.97 (0.91)</td>
<td>1.95 (0.92)</td>
</tr>
<tr>
<td>FEV1 (% pred)</td>
<td>56 (24)</td>
<td>57 (24)</td>
<td>56 (24)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.28 (1.12)</td>
<td>3.38 (1.21)</td>
<td>3.30 (1.21)</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>80 (21)</td>
<td>81 (22)</td>
<td>80 (22)</td>
</tr>
</tbody>
</table>

Before = hypertonic saline before airway clearance techniques, During = hypertonic saline during airway clearance techniques, After = hypertonic saline after airway clearance techniques, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity.
For spirometric data, the effect of one timing regimen in relation to another was reported as a mean between-group difference in the change from baseline to 2 hr post-baseline, with 95% CIs. Effects on efficacy, tolerability, and satisfaction were reported as mean between-group differences with 95% CIs. The number of participants reporting adverse events was calculated as percentages for each arm of the study. The number of participants who preferred each timing regimen was reported as a proportion. Adherence was calculated as the total number of airway clearance sessions performed divided by the total number of sessions scheduled, and reported as a percentage.

**Results**

**Flow of participants, therapists, centres through the study**

Fifty of the 52 patients approached about participation in the study gave consent and were eligible for the study. All 50 participants completed the three days of interventions as randomised. After completion of this initial data collection, each participant was followed for one year, during which 14 participants were re-admitted to hospital for a respiratory exacerbation. All 14 participants again met the eligibility criteria and agreed to repeat the three-day study. All 14 participants were re-admitted to hospital for a respiratory exacerbation. All 14 participants who repeated the study completed all 50 participants except their lung function was lower, which is consistent with their readmission to hospital. The mean time between both studies was 295 days.

For spirometric data, the effect of one timing regimen in relation to another was reported as a mean between-group difference in the change from baseline to 2 hr post-baseline, with 95% CIs. Effects on efficacy, tolerability, and satisfaction were reported as mean between-group differences with 95% CIs. The number of participants reporting adverse events was calculated as percentages for each arm of the study. The number of participants who preferred each timing regimen was reported as a proportion. Adherence was calculated as the total number of airway clearance sessions performed divided by the total number of sessions scheduled, and reported as a percentage.

**Compliance with the trial method**

According to sachet counts and hospital case records, all 50 participants undertook all interventions as allocated, except 2 (4%) participants. These 2 participants had been minimally productive of sputum after the first treatment session of the day and therefore elected a priori to undertake only the morning and afternoon treatment sessions on each study day. These participants performed two treatment sessions on each of the three study days and based their visual analogue scale reports on the two sessions of each timing regimen they experienced. Therefore adherence with the allocated sessions was 99% overall.

All 50 participants had complete datasets for efficacy, tolerability, and satisfaction. Due to the limited resources available for using a blinded assessor, only 32 participants were allocated to undergo spirometric data collection in accordance with the sample size calculation. All of these 32 participants had complete datasets for spirometric outcomes for all three study days.

All 14 participants who repeated the study completed all interventions as allocated and had complete datasets for all outcomes measured.

**Effect of intervention**

Group data for the measures of lung function are reported in Table 2. Individual data are presented in Table 3 (see eAddenda for Table 3). All measures of lung function in all groups exhibited a mean increase from baseline to 2 hours post-baseline. However, there were no substantial differences between the groups in the mean amount of improvement in lung function, with the between-group comparisons being either of borderline statistical significance or non-significant. The results with borderline statistical significance favoured hypertonic saline before physical airway clearance techniques.

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**Table 4. Mean (SD) of groups and mean (95% CI) difference between groups for perceived efficacy, tolerability and satisfaction.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Before (n = 50)</th>
<th>During (n = 50)</th>
<th>After (n = 50)</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Perceived efficacy (mm)</td>
<td>60 (23)</td>
<td>65 (25)</td>
<td>50 (22)</td>
</tr>
<tr>
<td></td>
<td>Tolerability (mm)</td>
<td>61 (23)</td>
<td>60 (25)</td>
<td>58 (24)</td>
</tr>
<tr>
<td></td>
<td>Satisfaction (mm)</td>
<td>66 (21)</td>
<td>61 (25)</td>
<td>46 (22)</td>
</tr>
</tbody>
</table>

Before = hypertonic saline before airway clearance techniques, During = hypertonic saline during airway clearance techniques, After = hypertonic saline after airway clearance techniques.
Group data for perceived efficacy, tolerability and satisfaction are reported in Table 4. Individual data are presented in Table 3 (see eAddenda for Table 3). Perceived efficacy was significantly lower when hypertonic saline was inhaled after airway clearance techniques, as opposed to before or during the techniques. Tolerability was not affected by the timing regimen used. Satisfaction with the entire airway clearance regimen was significantly lower when hypertonic saline was inhaled after airway clearance techniques, as opposed to before or during the techniques.

No adverse events were identified. No doses of hypertonic saline and no treatments with airway clearance techniques were missed due to poor tolerance.

The proportion of participants who preferred each timing regimen is presented in the first column of Figure 2. The largest proportion of participants (29/50, 58%) preferred hypertonic saline before airway clearance techniques, although hypertonic saline during the techniques was also popular (18/50, 36%). Few participants preferred hypertonic saline after the techniques (3/50, 6%). These proportions were very similar among the 14 participants who repeated the three-day study (see the first two columns of Figure 2), indicating that they were a representative sample of the original cohort of 50 participants with regard to their preferred regimen.

Among the 14 participants who repeated the three-day study, perceived efficacy, tolerability, and satisfaction were very similar to those reported during the initial study (data not shown) and again no adverse events occurred. Eleven of the 14 participants preferred the same timing regimen as in the initial 3-day study. The proportions of participants in the repeat study who preferred each regimen were very similar to the initial study (see the first and last columns of Figure 2).

**Discussion**

This study identified that the timing of hypertonic saline in relation to airway clearance techniques did not have a substantial effect on the change in lung function after a single treatment session. However, participants were more satisfied with the entire treatment session when hypertonic saline was inhaled before or during the airway clearance techniques. Similarly, these timing regimens were also perceived as more effective than inhaling hypertonic saline after the techniques. These differences in perceived effectiveness and satisfaction may have important implications for long-term adherence, which is known to be low for both hypertonic saline and airway clearance techniques (Abbott et al 2004, Elkins et al 2006b).

These results are likely to be valid because the study design incorporated several features to minimise the potential for bias in the results, such as concealed allocation and intention-to-treat analysis. Also, sample size calculations for the primary outcome and one secondary outcome were performed and the required cohorts were recruited. Furthermore, there was no loss to follow-up and compliance with the trial method was excellent. Potential bias was also reduced by blinding the assessors of the primary outcome. The stability of the results of this trial over time suggest that the initial results were not a chance finding.

Hypertonic saline is known to cause a drop in lung function in some people with cystic fibrosis that typically resolves by 15 min but persists in a small percentage of patients (Bye and Elkins 2007). Therefore, one limitation of this study was that the effect of the timing regimen on lung function was only measured at 2 hours after baseline and not 15 min after the inhalation. However, trying to measure lung function immediately after inhalation would have interrupted the entire treatment session on some days and not others, and this may have confounded the comparisons between the timing regimens. Measurement was therefore standardised at 2 hours, allowing valid comparisons and providing important information about sustained treatment effects. Another limitation of the study was that measures of mucus clearance were not included, which reduces the potential to understand the mechanism(s) at work in the different timing regimens. However, any differences in mucus clearance were too small to produce substantial differences in lung function. Therefore, the outcome measures used are adequate to guide treatment selection.

The effect of the timing regimens on FEV₁ was minor. Although some between-group comparisons were of borderline statistical significance, the mean differences and their 95% CIs were all well below 150 mL (the a priori smallest worthwhile effect), and equated to ≤ 2% of the predicted normal value. Therefore, although these borderline results favoured inhalation of hypertonic saline before airway clearance techniques, any differences between the effects of the timing regimens on FEV₁ are probably too small to be clinically important. However, in the long term, clinically worthwhile differences in lung function from the use of a particular timing regimen could occur – possibly through differences in clearance effects and differences in adherence. This could be investigated in future research.

For FVC, the between-group comparisons were again either of borderline statistical significance or were non-significant. However, unlike the narrow confidence intervals seen in
the FEV\textsubscript{1} data, some of the between-group comparisons for FVC had 95% CIs that did not exclude the possibility of substantial effects. For example, inhaling hypertonic saline before airway clearance techniques might increase the improvement in FVC by as much as 180 mL, more than inhaling it during or after the techniques. Therefore, further data could be obtained to make the estimate of the effect on FVC more precise and then to determine whether it is large enough to be clinically worthwhile. As with FEV\textsubscript{1}, the effect of long-term use of a timing regimen on FVC could also be investigated.

Perceived efficacy and satisfaction were significantly lower when hypertonic saline was inhaled after airway clearance techniques than with the other timing regimens. Inhalation of hypertonic saline after the techniques may fail to capitalise on effects of hypertonic saline on mucus clearance if techniques to promote expectoration are not undertaken until 4–6 hours later. Although these results were statistically significant, some may not be clinically worthwhile because the 95% CIs contain effects smaller than the \textit{a priori} smallest worthwhile effect of 10 mm on the 100 mm visual analogue scale. However, the effect of inhaling hypertonic saline before rather than after the techniques increased satisfaction by 20 mm (95% CI 12 to 29), which clearly exceeds the smallest worthwhile effect.

The data did not support our hypothesis that inhaling hypertonic saline after airway clearance techniques would reduce tolerability. We expected that inhaling the hypertonic saline after the techniques may have delivered it to a more exposed airway epithelium because the amount of overlying mucus would be minimised. However, this timing regimen did not reduce subjective or objective tolerability.

The absence of adverse events, the lack of intolerance, and the excellent adherence indicate that any of the three timing regimens is feasible among adults with CF who regularly use hypertonic saline and airway clearance techniques. However, this level of adherence may differ in the longer term or among users who are new to the interventions.

On the basis of these results, we suggest that clinicians should encourage adults with cystic fibrosis who use hypertonic saline and airway clearance techniques to inhale the saline before or during the techniques. A bronchodilator should be inhaled before the hypertonic saline. If dornase alpha is also to be used, it could be inhaled after the airway clearance techniques or at another time of the day, because these timing regimens do not reduce the benefit of dornase alpha (Dentice and Elkins 2011). Other medications such as inhaled antibiotics could be inhaled after airway clearance techniques, which theoretically would improve their deposition by reducing airway obstruction by mucus.

Footnotes: 1HYPERSAL 6, Royal Children's Hospital, Parkville, Australia, 2LC plus nebuliser, Pari, Hamburg, Germany, 3Ventolin, Allen & Hanburys, Boronia, Australia, 4Volumatic, Allen & Hanburys, Boronia, Australia, 5Easy-One, NDD Medical Technologies, Andover, USA.

eAddenda: Table 3 available at jop.physiotherapy.asn.au

Ethics: The Sydney Local Health District (RPAH Zone) Ethics Committee approved this study (X09-0283, HREC/09/RPAH/477). All participants gave written informed consent before data collection began.

Competing interests: None.

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Research


