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TABLE OF CONTENTS

[Intervention Review]

Timing of hypertonic saline inhalation for cystic fibrosis

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ABSTRACT

Background

Inhalation of hypertonic saline improves sputum rheology, accelerates mucociliary clearance and improves clinical outcomes of people with cystic fibrosis.

Objectives

To determine whether the timing of hypertonic saline inhalation (in relation to airway clearance techniques or in relation to time of day) has an impact on its clinical efficacy in people with cystic fibrosis.

Search methods

We identified relevant randomised and quasi-randomised controlled trials from the Cochrane Cystic Fibrosis Trials Register, the Physiotherapy Evidence Database (PEDro), and international cystic fibrosis conference proceedings.

Date of the last search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register: 19 December 2016.

Selection criteria

Any trial of hypertonic saline in people with cystic fibrosis where timing of inhalation was the randomised element in the study protocol with either: inhalation up to six hours before airway clearance techniques compared to inhalation during airway clearance techniques compared to inhalation up to six hours after airway clearance techniques; or morning compared to evening inhalation with any definition provided by the author.

Data collection and analysis

Both authors independently assessed the trials identified by the search for potential inclusion in the review.

Main results

The searches identified 97 trial reports which represented 46 studies, of which two studies (providing data on 63 participants) met our inclusion criteria. Both studies used a cross-over design. Both studies had low risk of all types of bias except the participants and the therapists who applied the treatments were not blinded. Intervention periods ranged from one treatment to three treatments in one day. The effects of the various regimens on lung function were non-significant. Satisfaction was rated significantly lower on a 100-mm scale when hypertonic saline was inhaled after the airway clearance techniques: mean differences 20.38 mm (95% confidence interval 12.10

to 28.66) compared to before airway clearance techniques and 14.80 mm (95% confidence interval 5.70 to 23.90) compared to during the techniques. Perceived effectiveness showed similar significant results. Other outcomes were unaffected by the timing regimen used. No trials compared morning versus evening inhalation of hypertonic saline.

Authors' conclusions

People with cystic fibrosis could be encouraged to inhale hypertonic saline before or during airway clearance techniques to maximise perceived efficacy and satisfaction, even though these timing regimens may not have any better effect on lung function than inhalation after airway clearance techniques. Given the long-term efficacy of hypertonic saline has only been established for twice-daily inhalations, clinicians should advise patients to inhale hypertonic saline twice daily. However, if only one dose per day is tolerated, the time of day at which it is inhaled could be based on convenience or tolerability until evidence comparing these regimens is available.

PLAIN LANGUAGE SUMMARY

The timing of inhalation of hypertonic saline in people with cystic fibrosis

Review question

We reviewed the evidence about whether the timing (in relation to airway clearance techniques or in relation to time of day) of hypertonic saline (a strong, sterile, salt water solution) through a nebuliser improves the physical properties of sputum, stimulates cough, improves clinical outcomes (such as lung function), and improves the perceived effect of airway clearance techniques in cystic fibrosis.

Background

Regular inhalation of hypertonic saline improves the clinical outcomes of people with cystic fibrosis. It is not certain whether it is better to inhale hypertonic saline before, during or after clearing the airways with physical techniques, nor whether it is better to inhale it in the morning or in the evening. We looked for trials that compared these different timing regimens.

Search date

The evidence is current to: 19 December 2016.

Study characteristics

The review included two studies with 63 people with cystic fibrosis aged between 18 and 64 years of age. The studies looked at the impact of the timing of hypertonic saline inhalation in relation to airway clearance techniques. The studies reported immediate outcomes after inhalation of hypertonic saline before, during or after physical airway clearance techniques. Both studies were short, involving only one to three treatments of each timing regimen.

Key results

While outcomes such as lung function did not show any difference between the regimens, people with cystic fibrosis perceived that inhaling hypertonic saline before or during airway clearance techniques was more effective and satisfying than inhaling hypertonic saline after airway clearance. No studies comparing morning and evening inhalation were found. Because the long-term efficacy of hypertonic saline has only been established for twice-daily inhalations, clinicians should advise patients to inhale hypertonic saline twice daily. However, if only one dose per day is tolerated, the time of day at which it is inhaled could be based on convenience or tolerability until further evidence is available.

Quality of the evidence

Overall, the quality of the evidence was very good. The only issues perhaps affecting the quality related to the fact that it was not possible for participants to be blinded to the treatment they received. However, because the studies were short-term and most of the significant results were based on perceived efficacy, timing of administration of hypertonic saline needs further study.

BACKGROUND

Description of the condition

Cysic fibrosis (CF) is the most common life-limiting autosomal recessive disorder amongst Caucasians (Cutting 2002). Mucociliary clearance is impaired in CF (Robinson 1996; Robinson 1997). Cystic fibrosis-related pulmonary disease is the major cause of morbidity and mortality (Buzzetti 2009).

Description of the intervention

Hypertonic saline is a sterile salt-water solution delivered as a nebulised therapy, usually at a concentration of between 3% and 10% (composition by mass). Traditionally, volumes of 3 mL to 10 mL are nebulised (Elkins 2006c; Wark 2009). Long-term use is recommended (Button 2016).

Each dose of hypertonic saline is usually nebulised immediately prior to airway clearance, but other timing regimens are sometimes used in clinical practice. The clinical effect of hypertonic saline could be affected by the timing of its delivery in relation to physical airway clearance techniques (before, during or after) or in relation to time of day (morning or evening).

How the intervention might work

Hypertonic saline has been shown to accelerate mucociliary clearance in the CF airway (Robinson 1996; Robinson 1997). Three mechanisms are believed to contribute to this improvement in mucociliary clearance. The first is restoration of the depleted airway surface liquid volume, which peaks almost immediately after a dose, but which may be sustained for several hours (Donaldson 2006). The other mechanisms are improvement in the rheology of the mucus (King 1997; Wills 1997), and stimulation of cough (Robinson 1996; Robinson 1997). The overall effect on mucus clearance is presumably responsible for the significant clinical improvements including lung function, quality of life, and ease of expectoration with regular use of the therapy (Elkins 2006b; Eng 1996). A Cochrane Review of nebulised hypertonic saline for CF concluded that improvements in forced expiratory volume at one second (FEV_1) were demonstrated over two to four weeks of therapy and quality of life and pulmonary exacerbation rates were improved compared to placebo interventions over 48 weeks of treatment (Wark 2009).

In the controlled studies that established the efficacy of hypertonic saline (Elkins 2006c; Eng 1996; Robinson 1996; Robinson 1997), each dose was nebulised immediately before the administration of airway clearance techniques. However, other timing regimens may have advantages. Nebulisation of hypertonic saline *during* airway clearance techniques could save time. It also may capitalise on the immediate peak in the airway surface liquid volume. 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 portion of the bronchial tree.

In the clinical trials that established the efficacy of the regular use of hypertonic saline (Donaldson 2006; Elkins 2006c; Eng 1996), at least two doses per day were used. However, some individuals can tolerate (or for other reasons elect to use) only one dose per day. For these people, nebulising the dose at a particular time of the day may affect its efficacy. Given that spontaneous mucociliary clearance is faster during waking hours than sleep (Bateman 1978), morning inhalation of hypertonic saline may capitalise on faster daytime mucociliary clearance and on the mucus-clearing effects of daytime activities such as exercise (Wolff 1977). Some people with CF find evening inhalation more convenient or report that it improves ease of expectoration the following morning. Since mucociliary clearance and coughing are suppressed overnight, evening inhalation of hypertonic saline may increase its dwell time in the airways, possibly increasing its clinical efficacy.

Why it is important to do this review

Despite the theoretical rationales presented to justify the investigation of alternative timing regimens in the previous section, it is also possible that they may have adverse effects on the efficacy, tolerability and convenience of the treatment and on the duration of the airway clearance session. For example, nebulisation of hypertonic saline during airway clearance techniques could increase the complexity of the overall session of airway clearance, perhaps requiring modified equipment. Nebulisation *after* airway clearance techniques presumably delivers the hypertonic saline more directly to the exposed airway epithelium, rather than an overlying mucus layer, which may reduce tolerability. Evening delivery may increase nocturnal coughing and sleep disturbance. Therefore, it is important to review well-designed research that compares the regimens.

There is a high treatment burden associated with CF for both people with the disease and for care providers. Hypertonic saline inhalation adds to the duration of the overall treatment regimen. Therefore, even if the various timing regimens have equal clinical efficacy, it is important that the review also investigates whether the interventions differ in their effects on the duration of the overall airway clearance session, in their convenience and in their side effects.

OBJECTIVES

To determine whether the timing of hypertonic saline inhalation, in relation to physical airway clearance techniques or time of day, has an impact on objective and subjective measures of clinical efficacy and tolerability in people with CF.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials (published and unpublished). Both random allocation and quasi-random allocation (e.g. where there is alternate allocation to groups) were included. Parallel and cross-over trials were eligible.

Types of participants

People of all ages and of both sexes with CF diagnosed by genetic testing or evidence on sweat chloride or nasal potential difference, including all degrees of disease severity.

Types of interventions

Nebulised hypertonic saline, where timing of inhalation was the randomised element in the study protocol:

1. hypertonic saline inhalation up to six hours before airway clearance techniques, compared to inhalation during airway clearance techniques;
2. hypertonic saline inhalation up to six hours before airway clearance techniques, compared to up to six hours after airway clearance techniques;
3. hypertonic saline inhalation during airway clearance techniques, compared to up to six hours after airway clearance techniques;
4. morning compared to evening inhalation with any definition provided by the author. If not defined, we accepted midnight to midday as morning and midday to midnight as evening.

Note: many individuals perform two treatments with physical airway clearance techniques each day. Even if these treatments are performed as far as possible from each other (i.e. 12 hours apart), any threshold greater than six hours would mean that the hypertonic saline labelled 'before' would actually be closer to 'after' the previous treatment with physical airway clearance techniques. Therefore, six hours is the broadest threshold possible to capture all potentially relevant trials. However, some of the mechanisms by which timing may affect the outcome are short-lived. Therefore, a sensitivity analysis is performed that only considers trials where the hypertonic saline is within 30 min of the techniques (*see* Sensitivity analysis).

The timing regimen could be a single treatment or could be maintained for any duration.

Hypertonic saline treatment had to be a minimum of a single dose of at least 3% concentration. If studies mentioned co-interventions (such as bronchodilators and other inhaled medications), these were permitted provided they were the same on all trial days and taken either before or after the period during which hypertonic saline and airway clearance techniques were used.

Airway clearance techniques (ACT) had to be a minimum of 10 minutes in duration and include at least one of the following:

1. postural drainage with percussion and vibration (PDPV). In other reviews this has been described as conventional chest physiotherapy (CCPT) (Elkins 2006c; Main 2009; van der Schans 2009);
2. active cycle of breathing techniques (ACBT).This comprises relaxation or breathing control, forced expiration technique (FET), thoracic expansion exercises and may include postural drainage or percussion (Robinson 2010);
3. autogenic drainage (AD). This breathing technique uses high expiratory flow rates at varying lung volumes to enhance mucus clearance while avoiding airway closure;
4. positive expiratory pressure (PEP) (Elkins 2006a);
5. oral oscillatory devices that provide oscillating PEP (such as the Flutter, Cornet and Acapella) or intrapulmonary percussive ventilation, which provides continuous oscillation of the air pressure in the airways via the mouth (Morrison 2009);
6. thoracic oscillating devices applied via a vest to provide external chest wall oscillation (Morrison 2009);
7. exercise prescribed for the purpose of airway clearance either independently or as an adjunct to other techniques.

Types of outcome measures

Primary outcomes

1. Lung function, i.e., change in lung function (measured in litres or % predicted). If change values are unavailable, final post-treatment values will be used. Values in litres and in % predicted will be analysed separately.
   - i) forced expiratory volume at one second (FEV_1)
   - ii) forced vital capacity (FVC)
2. Patient-reported outcomes, using validated scales or subjective reporting measures
   - i) measures of quality of life (QoL)
   - ii) symptom scores (including cough, tolerability, subjective ease of clearance, or treatment satisfaction)

Secondary outcomes

1. Measures of sputum clearance, including measures of mucociliary clearance (assessed by radioactive tracer clearance) and objective measures of sputum volume
2. Measures of exercise capacity (either maximal or submaximal where measured directly, or by a standard field test)
3. Mortality (all cause or CF-related, analysed separately)
4. Other pulmonary parameters
   i) forced expiratory flow between 25% and 75% of the vital capacity ($FEF_{25–75}$)
   ii) maximal instantaneous forced flow when 25% of the FVC remains to be exhaled (MEF_{25})
   iii) total lung capacity (TLC)
   iv) residual volume (RV)
   v) functional residual capacity (FRC)
   vi) lung clearance index (LCI)
5. Frequency of exacerbations of respiratory infection (where a clear definition is described demonstrating an increase in symptoms or a decline in pulmonary function)
   i) admission rates to hospital (defined as either number of inpatient hospital admissions or days as a hospital inpatient)
   ii) courses of IV antibiotics (whether received in hospital or in the home)
   iii) outpatient treatments (presentations to hospital, unscheduled visits to the doctor)
6. Adherence to inhaled therapies, airway clearance techniques, and other therapies
7. Adverse effects such as bronchospasm, cough and acute decline in pulmonary function

Search methods for identification of studies

Electronic searches

We identified relevant trials from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register using the term 'hypertonic saline'.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work was identified by searching the abstract books of relevant conferences, including the three major cystic fibrosis conferences: the International Cystic Fibrosis Conference, the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

Date of last search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register: 19 December 2016.

In addition, we searched the Physiotherapy Evidence Database (PEDro) (Maher 2003) and the WHO International Clinical Trials Registry Platform for all years available (Appendix 1; Appendix 2). Date of last search: 1 March 2014.

Searching other resources

We hand-searched the biennial Australia and New Zealand CF Conference Proceedings from 1995 to 2013.

We contacted trial authors, experts and manufacturers of hypertonic saline to identify additional trials.

We searched the reference lists of the included studies.

Data collection and analysis

Selection of studies

Both authors (RD, ME) independently selected the trials to be included in the review. We performed initial screening by title and abstract, and reviewed the full text for studies remaining after the initial screening phase. We resolved disagreements by discussion. We excluded irrelevant records and have presented the details of these excluded trials and the reasons for exclusion in tabular form (Characteristics of excluded studies).

Data extraction and management

Each author independently extracted data from the included studies using a standardised data extraction form. We resolved any disagreements by discussion. Where data were absent or difficult to interpret in the presented form, the authors contacted the trial investigators to gain the information required to evaluate risk of bias in the trial and to facilitate data analysis. Data extraction was also carried out at the editorial base for the Dentice trial given we (the Cochrane Review authors) are also two of the trial authors (Dentice 2012).

Assessment of risk of bias in included studies

We independently determined the risk of bias for each trial using published and unpublished data from the trial investigators, following the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions 5.1* (Higgins 2011). The risk of bias was also carried out at the editorial base for the Dentice trial given we (the Cochrane Review authors) are also two of the trial authors (Dentice 2012). We assessed the following domains as either low risk, unclear risk, or high risk of bias:

1. sequence generation;

2. allocation concealment;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data;
5. selective outcome reporting;
6. other sources of bias.

We resolved any disagreements by discussion. In addition, each author independently rated each trial on the PEDro Scale (Maher 2003; de Morton 2009), using published and unpublished data from the trial investigators. The PEDro Scale was chosen because it has acceptably high reliability for individual ratings and for consensus ratings (Maher 2003; Shiwa 2011). It has undergone extensive validation including convergent and construct validity and the appropriateness of the scoring system has been justified with Rasch analysis (de Morton 2009). The PEDro Scale is also widely used and understood by physiotherapists (Elkins 2013). The Cochrane Risk of Bias tool has reliability that ranges from poor to slight (Armijo-Olivo 2012; Hartling 2009; Hartling 2013).

Measures of treatment effect

For dichotomous data we planned to use the risk ratio (RR) with 95% confidence intervals (95% CIs) as a measure of treatment effect with an intention-to-treat analysis. An intention-to-treat analysis means that, where participants did not receive treatment as allocated, and where measures of outcomes were available, the analysis was performed as if participants received the treatment to which they were allocated. We considered a trial to have analysed by intention to treat if the report explicitly states that all participants received treatment or control conditions as allocated. Mortality and adverse events were the only dichotomous outcomes.

For continuous data we planned to record the difference in mean change from baseline and standard deviation (SD) (or standard errors (SE)) for each group, or the final group means and SDs if change data are unavailable. We planned to calculate a pooled estimate of treatment effect using the mean difference (MD) with 95% CIs.

However, given that both of the included trials were cross-over in design, we used the generic inverse variance method. Where the MD and SE of the MD were available, we entered these directly into the meta-analysis. Where only group means and SDs were available, we calculated the MD by subtraction of one group mean from the other. We imputed the SD of the differences from that obtained from the data in a similar trial, taking into account the paired nature of the data. We then calculated SEs using the formula: imputed SD / $\sqrt{n}$.

Unit of analysis issues

We incorporated data from cross-over trials into meta-analysis using the generic inverse variance method, involving expression of data in terms of the paired mean differences between treatments and their SE. We calculated these values either from paired individual patient data provided by authors, or by calculation of mean differences between interventions and their SE from means, SDs and P values reported in the manuscript (Elbourne 2002). We intended to combine data from parallel-designed trials with those from cross-over trials in the meta-analyses, but only cross-over trials were obtained. If necessary, we intended to calculate the SEs in parallel trials from the MDs between treatments and their CIs, but only cross-over trials were obtained.

Dealing with missing data

Where data were absent or difficult to interpret in the presented form, we contacted the trial investigators in an attempt to obtain the data in a form that would facilitate data analysis. Had we not been able to obtain the data, our plan was to analyse only the available data (available-case analysis). Additional data were obtained from the authors of the van Ginderdeuren trial (Van Ginderdeuren 2011).

Assessment of heterogeneity

We visually inspected forest plots for overlap of the CIs and estimated statistical heterogeneity using the I^2 value (Higgins 2003). Given that thresholds for the interpretation of I^2 can be misleading (since the importance of inconsistency depends on several factors) we chose a rough guide to interpretation as follows: moderate heterogeneity was defined as an I^2 value of 30% to 60%, substantial heterogeneity was defined as an I^2 value of 50% to 90%, and considerable heterogeneity was defined as an I^2 value of 75% to 100%. The P value from the chi-squared test was also used to interpret the importance of the observed value of I^2. Clinical heterogeneity was also assessed by considering differences in trial designs and participants characteristics.

Assessment of reporting biases

If we had included sufficient trials in the review, we planned to assess publication bias using a funnel plot. If we suspected outcome reporting bias, we planned to contact trial investigators to clarify whether they measured and analysed certain outcomes and obtained the data. However, only two eligible trials were obtained; this was fewer than the recommended number of studies to construct a funnel plot so we were unable to assess whether outcome reporting bias was likely.

Data synthesis

We analysed the following between-group comparisons where possible:

1. hypertonic saline inhalation up to six hours before airway clearance techniques, compared to inhalation during airway clearance techniques;

2. hypertonic saline inhalation up to six hours before airway clearance techniques, compared to up to six hours after airway clearance techniques;

3. hypertonic saline inhalation during airway clearance techniques, compared to up to six hours after airway clearance techniques;

4. morning compared to evening inhalation with any definition provided by the author. If not defined, we accepted midnight to midday as morning and midday to midnight as evening.

We performed meta-analyses using a fixed-effect model. However, if we had observed substantial heterogeneity, we planned to use a random-effects model. We planned to further explore heterogeneity in the planned subgroup analyses.

Subgroup analysis and investigation of heterogeneity

We planned a subgroup analysis for different concentrations of hypertonic saline inhalation: low hypertonic concentrations (3% to 5%); medium (6% to 7%); and high (8% to 10%). We also planned to perform a subgroup analysis for intervention duration: less than two weeks; two to eight weeks; and greater than eight weeks. However, the included studies did not permit these analyses.

Sensitivity analysis

We planned to conduct sensitivity analyses to assess the robustness of the review results by repeating the analyses with the following adjustments:

- exclusion of trials with unclear or inadequate sequence generation;
- exclusion of trials with unclear or inadequate allocation concealment;
- exclusion of trials that scored less than 5 out of 10 on the PEDro Scale (Maher 2003);
- modifying the definition of 'before' and 'after' airway clearance techniques to within 30 minutes of the techniques;
- with and without cross-over trials.

However, the included studies did not permit these analyses.

RESULTS

Description of studies

Results of the search

The searches identified 97 trial reports which represented 46 studies.

Included studies

Two trials were eligible for inclusion, which provided data for a total of 63 participants (Dentice 2012; Van Ginderdeuren 2011) (Figure 1). One trial has not yet been published in full but has been presented as an oral presentation at a conference (Van Ginderdeuren 2011). No trial was identified regarding timing of hypertonic saline inhalation in relation to time of day.

Trial characteristics

The two included studies were randomised, cross-over trials with concealed allocation, intention to treat analysis and blinded assessors (Dentice 2012; Van Ginderdeuren 2011). They investigated the impact of timing of hypertonic saline inhalation in relation to airway clearance techniques. The inhalation blocks were for one day. In one trial, three treatments of the allocated timing regimen were performed on each of the three trial days (Dentice 2012). In the second trial, a single treatment of 30 minutes was undertaken on each of the three trial days (Van Ginderdeuren 2011). One day was solely autogenic drainage and did not include hypertonic saline inhalation. This arm of the trial was not relevant to the study question of this review so the data were not included.

Participants

Clarification of participant data was requested from the authors of the two studies. One trial included 50 adults (mean (SD) age 31 (10) years, range 18 to 64 years) with a confirmed diagnosis of cystic fibrosis who were clinically stable with an FEV_1 within 10% of the best recorded value in the last six months (Dentice 2012). This trial excluded people who were: hypertonic saline naïve or previously intolerant; lung transplant recipients; colonised with *Burkholderia cepacia* complex; not clinically stable; experienced haemoptysis greater than 60 mL within the last month or thrombocytopenia or pregnancy. The second trial recruited 13 hospitalised participants who were over 14 years (mean age 27 years, range 18 to 37 years) (Van Ginderdeuren 2011). All were productive daily and performed autogenic drainage for their airway clearance. The lung function of participants was not stated but some were noted to be on oxygen therapy. One participant withdrew after the first arm of the trial and therefore did not provide any cross-over data that could be included in the analysis.

Interventions

One trial administered 4 mL of 6% hypertonic saline via an LC Star (PARI, Germany) nebuliser three times per day with the allocated timing regimen for that day (Dentice 2012). Hypertonic saline was nebulised immediately before or after airway clearance, or during airway clearance with blocks of inhalation and pauses for airway clearance. Participants using positive expiratory pressure (PEP) devices were not permitted to administer hypertonic

saline simultaneously as this alters the inhaled dose and the distribution of the deposition (Laube 2005). The airway clearance technique was optimised for each participant on recruitment to the trial and was standardised for all three trial days. The second trial administered 4 mL of 6% hypertonic saline before or during 30 minutes of autogenic drainage (Van Ginderdeuren 2011).
The use of co-interventions (such as bronchodilators and other inhaled medications) was not reported in the studies (Dentice 2012; Van Ginderdeuren 2011).

Outcomes measures

One trial measured the change in FEV_1 and FVC (in litres and percentage of the predicted value) recorded prior to and two hours following the middle treatment session of each trial day (Dentice 2012). Symptom scores at the end of each intervention arm were also recorded: perceived effectiveness; tolerability; and satisfaction rated on a 100-mm visual analogue scale. Adverse events and adherence were also recorded. At the conclusion of the three-day trial, participants reported their preferred timing regimen.
The second trial reported the change in dyspnoea scores at the conclusion of each intervention arm, wet weight of sputum in grams produced during the treatment session, and adverse events and adherence (Van Ginderdeuren 2011).

Excluded studies

Of the remaining 44 studies identified through our search strategy, two were excluded because they did not involve the administration of hypertonic saline at all. A further 41 studies were excluded because the interventions they compared did not differ in the timing of hypertonic saline inhalation (Excluded studies).
The remaining trial, published as an abstract only, is included within 'Studies awaiting classification' and will be further assessed when the full paper is published (O'Neil 2016).

Risk of bias in included studies

Please refer to Figure 1; Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

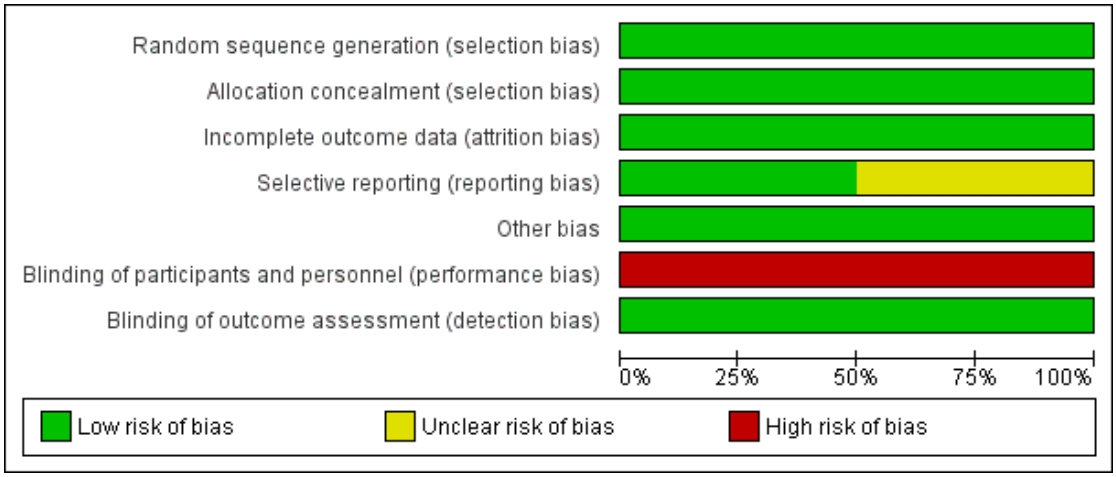
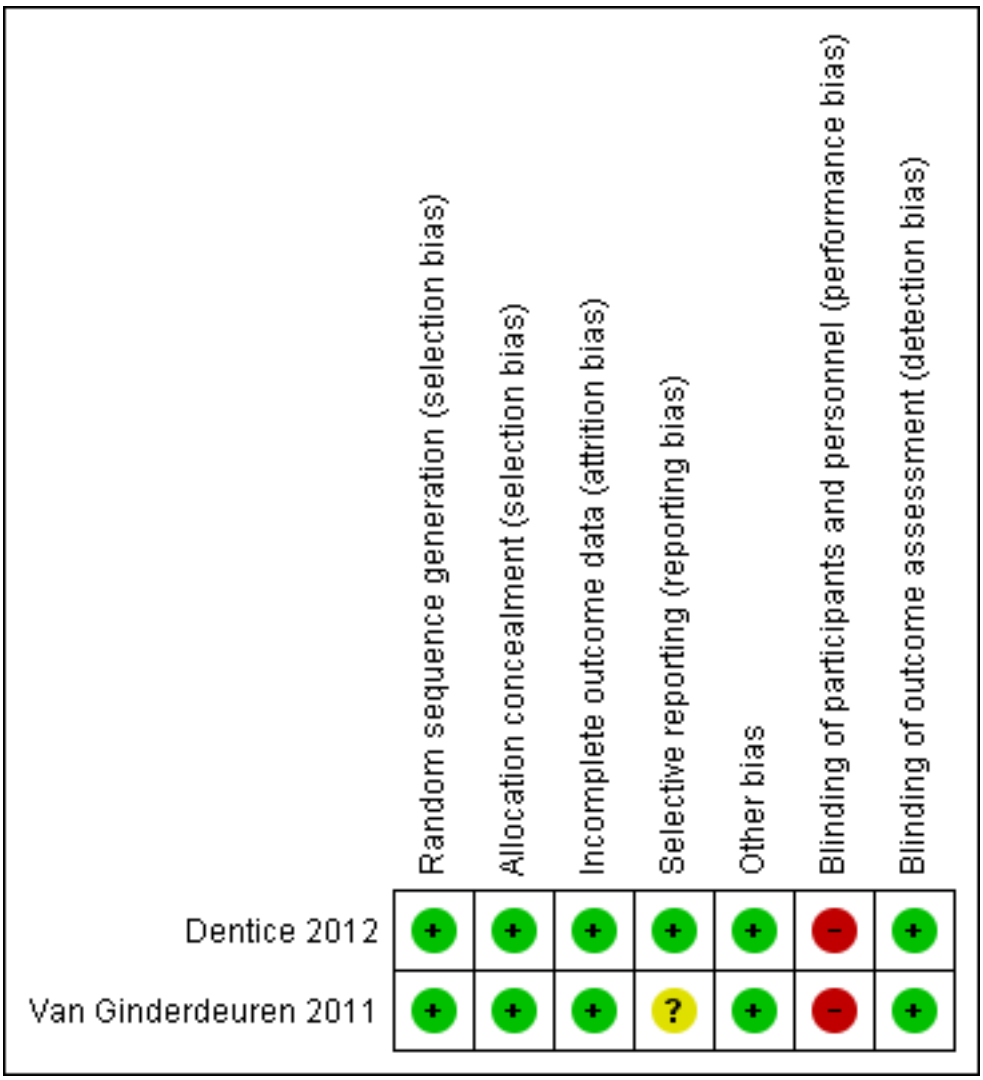


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Generation of sequence

Both trials reported adequate methods of random generation of the allocation sequence: computer-generated list (Dentice 2012) and allocations drawn from a box that had been shaken (Van Ginderdeuren 2011). Thus, the overall risk of bias due to the method of generation of the random sequence was low.

Concealment of allocation

Both trials reported using sealed opaque envelopes, so the overall risk of bias due to the non-concealment of allocation was low.

Blinding

In both trials, participants were not blinded to the timing regimen, leading to a high risk of bias. In both trials, outcome assessors were blinded to the timing regimen, leading to a low risk of bias.

Incomplete outcome data

Both trials reported all available data. One trial stated no withdrawals occurred (Dentice 2012) and the other stated that one participant withdrew after the first arm of the trial and therefore did not provide any cross-over data that could be included in the analysis (Van Ginderdeuren 2011) so analysis was conducted with all available data from 12 out of 13 participants (92%). Therefore, the overall risk of bias due to attrition was low.

Selective reporting

One trial was prospectively registered and remained consistent with this protocol (Dentice 2012). The second trial was not registered (Van Ginderdeuren 2011). The overall risk of bias was unclear.

Other potential sources of bias

No other potential sources of bias were identified.
Both of the trials met the external validity criterion of the PEDro score by stating both the source of participants and the eligibility criteria. Both trials met eight of the ten internal validity criteria on the PEDro score, with neither trial blinding participants or therapists.

Effects of interventions

Inhalation before versus during airway clearance techniques

Two studies with a total of 63 participants contributed data to this comparison (Dentice 2012; Van Ginderdeuren 2011).

Primary outcomes

1. Lung function

a. FEV

One trial provided data for this outcome (Dentice 2012). The change in FEV_1 from immediately before a treatment to two hours later was higher on average when hypertonic saline was inhaled before airway clearance techniques, with a MD of 0.04 litres (95% CI 0.00 to 0.08) (Analysis 1.1). However, this difference was not statistically significant when analysed using % predicted data (Analysis 1.2).

b. FVC

One trial provided data for this outcome (Dentice 2012). The change in FVC from immediately before a treatment to two hours later was not statistically significantly different between trial arms when analysed using data in litres (Analysis 1.3). However, change in FVC from immediately before a treatment to two hours later was higher on average when hypertonic saline was inhaled before airway clearance techniques when analysed using % predicted data, with a MD of 2.09% pred (95% CI 0.08 to 4.11) (Analysis 1.4).

2. Patient-reported outcomes

a. QoL

No trial reported this outcome.

b. Symptom scores

Two studies with a total of 63 participants contributed data to this comparison (Dentice 2012; Van Ginderdeuren 2011), but the symptom scores used were different so no meta-analysis was possible.
One trial provided data from 50 participants for perceived efficacy (i.e. ease of clearance), tolerability, and satisfaction, each recorded on a 10-cm visual analogue scale (Dentice 2012). There were no significant differences in any of these outcomes when hypertonic saline was inhaled before versus during airway clearance techniques (Analysis 1.5; Analysis 1.6; Analysis 1.7).
The second trial provided data from 12 participants for dyspnoea severity (Van Ginderdeuren 2011). There was no significant difference in dyspnoea when hypertonic saline was inhaled before versus during airway clearance techniques (Analysis 1.8).

Secondary outcomes

1. Measures of sputum clearance

One trial provided data from 12 participants for wet weight of sputum (Van Ginderdeuren 2011). There was no significant difference in the wet weight of sputum when hypertonic saline was inhaled before versus during airway clearance techniques (Analysis 1.9).

2. Measures of exercise capacity

No trial reported this outcome.

3. Mortality

No trial reported this outcome.

4. Other pulmonary parameters

No trial reported any of the other pulmonary parameters listed in the protocol.

5. Frequency of exacerbations of respiratory infection

No trial reported this outcome.

6. Adherence to inhaled therapies, airway clearance techniques, and other therapies

There was 100% compliance with all the single doses of each treatment under supervision in both studies (Dentice 2012; Van Ginderdeuren 2011).

7. Adverse effects such as bronchospasm, cough and acute decline in pulmonary function

There were no adverse events in either trial (Dentice 2012; Van Ginderdeuren 2011).

Inhalation before versus after airway clearance techniques

One trial with 50 participants contributed data to this comparison (Dentice 2012).

Primary outcomes

1. Lung function (absolute change and change in per cent predicted if possible, otherwise final values)

a. FEV

The change in FEV from immediately before a treatment to two hours later was not significantly influenced by whether hypertonic saline was inhaled before or after airway clearance techniques, whether analysed using data in litres (Analysis 2.1) or % predicted (Analysis 2.2).

b. FVC

The change in FVC from immediately before a treatment to two hours later was not significantly influenced by whether hypertonic saline was inhaled before or after airway clearance techniques, whether analysed using data in litres (Analysis 2.3) or % predicted (Analysis 2.4).

2. Patient-reported outcomes

a. QoL

No trial reported this outcome.

b. Symptom scores

Perceived efficacy (i.e. ease of clearance) was rated statistically significantly better when hypertonic saline was inhaled before versus after airway clearance techniques, MD 10.62 mm (95% CI 2.54 to 18.70) (Analysis 2.5)

Tolerability was not rated significantly differently when hypertonic saline was inhaled before versus after airway clearance techniques (Analysis 2.6).

Satisfaction was rated significantly better when hypertonic saline was inhaled before versus after airway clearance techniques, MD 20.38 mm (95% CI 12.10 to 28.66) (Analysis 2.7).

Secondary outcomes

1. Measures of sputum clearance

No trial reported this outcome.

2. Measures of exercise capacity

No trial reported this outcome.

3. Mortality

No trial reported this outcome.

4. Other pulmonary parameters

No trial reported this outcome.

5. Frequency of exacerbations of respiratory infection

No trial reported this outcome.

6. Adherence to inhaled therapies, airway clearance techniques, and other therapies

There was 100% compliance with all the single doses of each treatment.

7. Adverse effects such as bronchospasm, cough and acute decline in pulmonary function

There were no adverse events in the trial.

Inhalation during versus after airway clearance techniques

One trial with 50 participants contributed data to this comparison (Dentice 2012).

Primary outcomes

1. Lung function

a. FEV

The change in FEV_1 from immediately before a treatment to two hours later was not significantly influenced by whether hypertonic saline was inhaled before or after airway clearance techniques, whether analysed using data in litres (Analysis 3.1) or % predicted (Analysis 3.2).

b. FVC

The change in FVC from immediately before a treatment to two hours later was not significantly influenced by whether hypertonic saline was inhaled before or after airway clearance techniques, whether analysed using data in litres (Analysis 3.3) or % predicted (Analysis 3.4).

2. Patient-reported outcomes

a. QoL

No trial reported this outcome.

b. Symptom scores

Perceived efficacy (i.e. ease of clearance) was rated significantly better when hypertonic saline was inhaled during versus after airway clearance techniques, MD 15.60 mm (95% CI 17.55 to 23.65) (Analysis 3.5).
Tolerability was not rated significantly differently when hypertonic saline was inhaled during versus after airway clearance techniques (Analysis 3.6).
Satisfaction was rated significantly better when hypertonic saline was inhaled during versus after airway clearance techniques, MD 14.80 mm (95% CI 65.70 to 23.90) (Analysis 3.7).

Secondary outcomes

1. Measures of sputum clearance

No trial reported this outcome.

2. Measures of exercise capacity

No trial reported this outcome.

3. Mortality

No trial reported this outcome.

4. Other pulmonary parameters

No trial reported this outcome.

5. Frequency of exacerbations of respiratory infection

No trial reported this outcome.

6. Adherence to inhaled therapies, airway clearance techniques, and other therapies

There was 100% compliance with all the single doses of each treatment.

7. Adverse effects such as bronchospasm, cough and acute decline in pulmonary function

There were no adverse events in the trial.

Morning versus evening inhalation

No trial reported on this comparison.

DISCUSSION

Summary of main results

The searches identified 47 studies, of which two studies were eligible for inclusion - providing data for 63 participants. Both studies used a cross-over design. Intervention periods were short, so the overnight washout periods were probably appropriate. One trial provided three treatments in one day for each arm of the trial (Dentice 2012). The other provided a single treatment for each arm of the trial on separate days (Van Ginderdeuren 2011).

There were no clinically important differences between the timing regimens of before, during or after airway clearance techniques in the mean amount of improvement in lung function, with the between-group comparisons being non-significant (Dentice 2012). Perceived efficacy was between 10 and 20 mm lower on a 100-mm scale when hypertonic saline was inhaled after physical airway clearance techniques, as opposed to before or during the techniques (Dentice 2012). Tolerability was not affected by the timing regimen used (Dentice 2012). There was no significant difference in dyspnoea or sputum wet weight when hypertonic saline was inhaled before or during physical airway clearance techniques (Van Ginderdeuren 2011). Satisfaction with the entire airway clearance regimen was significantly lower when hypertonic saline was inhaled after physical airway clearance techniques, as opposed to before or during the techniques (Dentice 2012).

Overall completeness and applicability of evidence

No trials were found comparing morning versus evening inhalation of hypertonic saline. No trials were found in paediatric populations. Recommendations of the review are therefore limited to timing of inhalation in relation to airway clearance techniques in adults.

Quality of the evidence

Most potential sources of bias were assessed to be low risk, except blinding - with neither of the included trials blinding participants or therapists. It is often difficult for trials of physical interventions to achieve blinding, but was achieved in most of the trials in the Cochrane Review of timing of dornase alpha (Dentice 2012) using a double-dummy method. It is disappointing that neither of the included trials used this method to achieve blinding.

Agreements and disagreements with other studies or reviews

Although two eligible trials were found comparing timing regimens for hypertonic saline in relation to airway clearance techniques in adults, none of the outcomes were present in both trials. Interpretation of the data should therefore recognise that the findings have not been replicated in independent studies. However, one of the included studies did repeat the data collection on 14 participants within one year of doing the trial (Dentice 2012), with very similar results to the original data collected on the 50 participants.

The data identified by this review support the traditional approach of inhalation of hypertonic saline before airway clearance techniques, as has been used in previous studies demonstrating the efficacy of hypertonic saline for people with cystic fibrosis (Elkins 2006c; Eng 1996; Robinson 1996; Robinson 1997). However, the data also suggest that inhalation during airway clearance may be equally effective.

When advising about inhalation of hypertonic saline in relation to time of day, what issues might be considered in the absence of direct comparisons of different timing regimens of hypertonic saline? The trials demonstrating the efficacy of regular hypertonic saline have prescribed at least two doses per day (Donaldson 2006; Elkins 2006c; Eng 1996). The effect of single daily dosing on clinical outcomes is not known. Several studies suggest that as the dose of salt received is reduced, there is a reduction in hypertonic saline's effect on sputum rheology (King 1997; Wills 1997), mucociliary clearance (Robinson 1997), and perhaps some clinical outcomes (Elkins 2006d). Therefore, individuals should be encouraged to take doses twice daily if tolerated; however, for those who only tolerate one dose per day and elect to pursue this regimen, a choice about diurnal timing must be made. In the absence of a randomised comparison of morning versus evening inhalation, individual factors such as convenience, compliance, and tolerability could be considered. For example, if an individual has a hectic morning schedule and spare time after their day's activities, evening inhalation may be more convenient. Conversely, if individuals note increased nocturnal coughing and sleep disturbance with evening inhalation, morning inhalation may be better tolerated.

AUTHORS' CONCLUSIONS

Implications for practice

The two included studies identified that the timing of hypertonic saline in relation to physical airway clearance techniques did not have a substantial effect on the change in lung function, sputum wet weight or dyspnoea after a single treatment session. However, participants were more satisfied with the entire treatment session when hypertonic saline was inhaled before or during the physical airway clearance techniques - presumably because these timing

regimens were perceived as more effective than inhaling hypertonic saline after the techniques. This may have important implications for long-term adherence, which is known to be low for both hypertonic saline and physical airway clearance techniques (Abbott 2004; Elkins 2006b).

Perceived efficacy and satisfaction were lower when hypertonic saline was inhaled after physical airway clearance techniques than with the other timing regimens. Inhalation of hypertonic saline after the physical techniques may fail to capitalise on effects of hypertonic saline on mucus clearance if techniques to promote expectoration are not undertaken until four to six hours later.

On the basis of these results, we suggest that clinicians should encourage adults with cystic fibrosis who use hypertonic saline and physical airway clearance techniques to inhale the saline before or during the physical techniques. The hypertonic saline should also be inhaled after a bronchodilator as was the protocol in the two included trials, because it has previously been established that this is necessary to prevent bronchoconstriction (Bye 2007).

This review did not identify any evidence comparing the timing of hypertonic saline inhalation in relation to time of day. Until such evidence becomes available, clinicians could advise patients to inhale hypertonic saline twice daily; but if only one dose per day is tolerated, the time of day at which it is inhaled could be based on convenience or tolerability.

Implications for research

Any effect of the timing regimens on forced expiratory volume at one second (FEV_1) was minor. The mean differences and their 95% confidence intervals (CIs) were all well below 150 mL (the a priori smallest worthwhile effect in the Dentice 2012 trial), and equated to approximately 1% of the predicted normal value. Therefore, although the mean results favoured inhalation of hypertonic saline before physical airway clearance techniques, any effects of the timing regimens on FEV_1 are probably too small to be clinically important. However, unlike the narrow confidence intervals seen in the FEV_1 data, some of the between-group comparisons for forced vital capacity (FVC) had much wider 95% CIs, suggesting that further research could modify the estimate. For example, inhaling hypertonic saline before physical 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 one timing regimen has a clinically important benefit over another.

In addition, the trials were all of very short intervention periods, so longer-term research could be conducted to establish the effects arising from regular use, which would incorporate the influence of changes in adherence with long-term use, as well as generating data on any adverse effects that occur with long-term use.

Although we did not include "duration of the entire airway clearance session (i.e. including aerosol delivery and physical airway clearance techniques)" as an outcome in this review, we note that neither of the included studies reported this outcome. We acknowledge that this outcome is an important consideration. We will amend the protocol for this review before the next update is commenced to include this important outcome.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dentice 2012

Methods	Randomised, cross-over trial with concealed allocation, intention-to-treat analysis and blinded assessors; investigating the impact of timing of hypertonic saline inhalation in relation to airway clearance techniques. The inhalation blocks were for one day. The three treatments of the allocated timing regimen were performed on each of the three trial days, with no washout day
Participants	50 adults (mean age 31 years, SD 10, range 18 - 64 years) with a confirmed diagnosis of cystic fibrosis who were clinically stable with an FEV_1 within 10% of the best recorded value in the last 6 months. This trial excluded people who were hypertonic saline naïve or previously intolerant, a lung transplant recipient, colonised with *Burkholderia cepacia* complex, not clinically stable, haemoptysis greater than 60 mL within the last month, thrombocytopenia or pregnancy
Interventions	4 mL of 6% hypertonic saline was nebulised via an LC Star nebuliser 3 times per day with the allocated timing regimen for that day. Hypertonic saline was nebulised immediately before or after airway clearance or during (with blocks of inhalation and pauses for airway clearance). The airway clearance technique was optimised for each participant on recruitment to the trial and was standardised for all 3 trial days
Outcomes	The primary outcome was the change in FEV_1 and FVC (in litres and percentage of the predicted value) recorded prior to and two hours following the middle treatment session of each trial day. Symptom scores at the end of each intervention arm were also recorded: perceived effectiveness, tolerability and satisfaction rated on a 100 mm visual analogue scale. Adverse events and adherence were also recorded
Notes	PEDro Score: 8/10 [Eligibility criteria: yes; random allocation: yes; concealed allocation: yes; baseline comparability: yes; blind participants: no; blind therapists: no; blind assessors: yes; adequate follow up: yes; intention-to-treat analysis: yes; Between-group comparisons: yes; point estimates and variability: yes. Note: eligibility criteria item does not contribute to total score]

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation list.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Stated "no withdrawals" and intention-to-treat analysis used

Dentice 2012 (*Continued*)

Selective reporting (reporting bias)	Low risk	Consistent with the prospectively registered trial protocol.
Other bias	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were unblinded to the timing regimen.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.

Van Ginderdeuren 2011

Methods	Randomised, cross-over trial with concealed allocation, intention to treat analysis and blinded assessors; investigating the impact of timing of hypertonic saline inhalation in relation to airway clearance techniques. The inhalation blocks were for one day. The two treatment days that contributed data to this review involved single treatment of 30 minutes with differing timing of hypertonic saline in relation to physiotherapy airway clearance techniques (i.e. hypertonic saline before or during autogenic drainage). The other day was solely autogenic drainage and did not include hypertonic saline inhalation, so it is not discussed further in this review
Participants	13 hospitalised participants who were over 14 years (mean age 27 years, range 18 - 37 years). All were productive daily and performed autogenic drainage for their airway clearance. The lung function of participants was not stated but some were noted to be on oxygen therapy. One participant withdrew and outcome data was not included in analysis
Interventions	4 mL of 6% hypertonic saline before or during 30 minutes of autogenic drainage. The type of nebuliser and use of co-interventions were not reported
Outcomes	Outcomes included change in dyspnoea scores at the conclusion of each intervention arm, wet weight of sputum in grams produced during the treatment session, and adverse events and adherence
Notes	PEDro Score: 8/10 [Eligibility criteria: yes; random allocation: yes; concealed allocation: yes; baseline comparability: yes; blind participants: no; blind therapists: no; blind assessors: yes; adequate follow up: yes; intention-to-treat analysis: yes; between-group comparisons: yes; point estimates and variability: yes. Note: eligibility criteria item does not contribute to total score]

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Van Ginderdeuren 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	Allocations were drawn from a box after the box had been shaken
Allocation concealment (selection bias)	Low risk	Allocations were sealed in opaque envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant was lost to follow up but intention to treat analysis was conducted
Selective reporting (reporting bias)	Unclear risk	No registered protocol. No protocol available from the author
Other bias	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were unblinded to the timing regimen.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.

FEV_1 : forced expiratory volume at one second
FVC: forced vital capacity
SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adde 2004	Intervention not related to the timing of hypertonic saline inhalation
Amin 2010	Intervention not related to the timing of hypertonic saline inhalation
Amin 2016	Intervention not related to the timing of hypertonic saline inhalation
Aquino 2012	Intervention not related to the timing of hypertonic saline inhalation
Balinotti 2015	Intervention not related to the timing of hypertonic saline inhalation
Ballmann 2002	Intervention not related to the timing of hypertonic saline inhalation
Brivio 2013	Intervention not related to the timing of hypertonic saline inhalation

(*Continued*)

Brown 2010	Intervention not related to the timing of hypertonic saline inhalation
Buonpensiero 2010	Intervention not related to the timing of hypertonic saline inhalation
Cardinale 2003	Intervention not related to the timing of hypertonic saline inhalation
Chadwick 1997	Intervention not related to the timing of hypertonic saline inhalation
De Cono 2008	Intervention not related to the timing of hypertonic saline inhalation
Dentice 2013	Intervention not related to the timing of hypertonic saline inhalation
Donaldson 2003	Intervention not related to the timing of hypertonic saline inhalation
Donaldson 2006	Intervention not related to the timing of hypertonic saline inhalation
Donaldson 2013	Intervention not related to the timing of hypertonic saline inhalation
Dwyer 2013	Intervention not related to the timing of hypertonic saline inhalation
Elkins 2006c	Intervention not related to the timing of hypertonic saline inhalation
Elkins 2006d	Intervention not related to the timing of hypertonic saline inhalation
Eng 1996	Intervention not related to the timing of hypertonic saline inhalation
Furnari 2012	Intervention not related to the timing of hypertonic saline inhalation
Grasemann 2005	Did not involve administration of hypertonic saline.
Grasemann 2013	Did not involve administration of hypertonic saline.
Grieve 2003	Intervention not related to the timing of hypertonic saline inhalation
Gupta 2012	Intervention not related to the timing of hypertonic saline inhalation
Herrero 2016	Intervention not related to the timing of hypertonic saline inhalation
Hofmann 1997	Intervention not related to the timing of hypertonic saline inhalation
Homola 2013	Intervention not related to the timing of hypertonic saline inhalation
Kobylyansky 2000	Intervention not related to the timing of hypertonic saline inhalation
Laube 2009	Intervention not related to the timing of hypertonic saline inhalation

(*Continued*)

Mainz 2015	Intervention not related to the timing of hypertonic saline inhalation
Palacio 2014	Intervention not related to the timing of hypertonic saline inhalation
Riedler 1996	Intervention not related to the timing of hypertonic saline inhalation
Robinson 1996	Intervention not related to the timing of hypertonic saline inhalation
Robinson 1997	Intervention not related to the timing of hypertonic saline inhalation
Robinson 1999	Intervention not related to the timing of hypertonic saline inhalation
Ros 2012	Intervention not related to the timing of hypertonic saline inhalation
Rosenfeld 2012	Intervention not related to the timing of hypertonic saline inhalation
Ruiz 2012	Intervention not related to the timing of hypertonic saline inhalation
Suri 2002	Intervention not related to the timing of hypertonic saline inhalation
Suri 2007	Intervention not related to the timing of hypertonic saline inhalation
Teper 2012	Intervention not related to the timing of hypertonic saline inhalation
Vanlaethem 2008	Intervention not related to the timing of hypertonic saline inhalation

Characteristics of studies awaiting assessment *[ordered by study ID]*

O'Neil 2016

Methods	Randomised cross-over trial. The physiotherapist collecting the outcome measures was blinded
Participants	14 adults with CF recruited, 13 completed the trial (mean (SD) age 33 years (12), FEV_1 % predicted 51 (22), LCI (no. turnovers) 14 (4))
Interventions	ACTs after HTS inhalation or ACTs during HTS inhalation on alternate days. Between days 10 - 14 of intravenous antibiotic course during a pulmonary exacerbation. ACT treatment consisted of 10 cycles of active cycle of breathing technique using an Acapella®.
Outcomes	Participants completed a multiple breath washout (MBW) test to obtain LCI and spirometry (FEV_1) at baseline and 90 min post treatment. Sputum collection during 90 min, ease of clearance and satisfaction with treatment was also recorded. Wilcoxon test was used and $P < 0.05$ was considered significant
Notes	Abstract only.

ACTs: airways clearance techniques
CF: cystic fibrosis

FEV_1 : forced expiratory volume in one second
HTS: hypertonic saline
LCI: lung clearance index
SD: standard deviation

DATA AND ANALYSES

Comparison 1. Inhalation before versus during airway clearance techniques

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV_1 (L)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
2 FEV_1 (% pred)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
3 FVC (L)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
4 FVC (% pred)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
5 Perceived efficacy (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
6 Tolerability (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
7 Satisfaction (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
8 Dyspnoea	1		Mean Difference (Fixed, 95% CI)	Totals not selected
9 Sputum wet weight	1		Mean Difference (Fixed, 95% CI)	Totals not selected

Comparison 2. Inhalation before versus after airway clearance techniques

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV_1 (L)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
2 FEV_1 (% pred)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
3 FVC (L)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
4 FVC (% pred)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
5 Perceived efficacy (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
6 Tolerability (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
7 Satisfaction (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected

Comparison 3. Inhalation during versus after airway clearance techniques

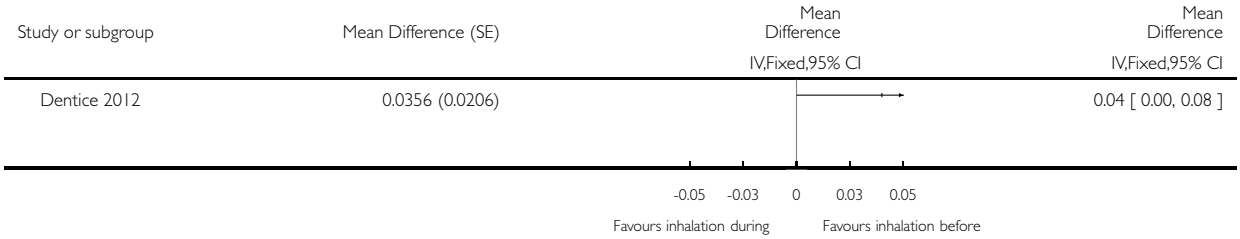
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV_1 (L)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
2 FEV_1 (% pred)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
3 FVC (L)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
4 FVC (% pred)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
5 Perceived efficacy (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
6 Tolerability (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
7 Satisfaction (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 1 FEV_1 (L).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 1 Inhalation before versus during airway clearance techniques

Outcome: 1 FEV_1 (L)

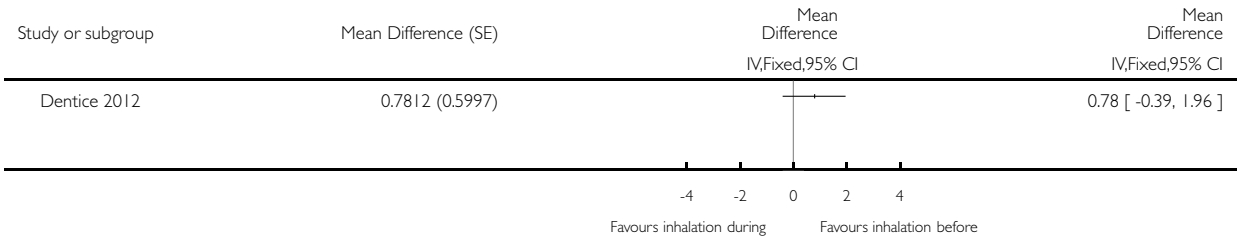


Analysis 1.2. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 2 FEV_1 (% pred).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 1 Inhalation before versus during airway clearance techniques

Outcome: 2 FEV_1 (% pred)

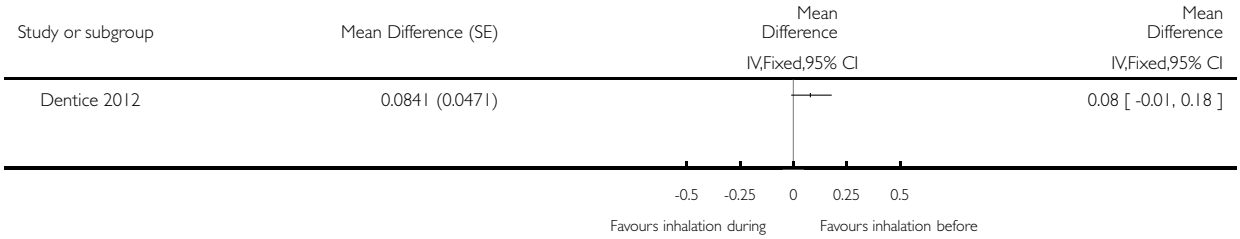


Analysis 1.3. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 3 FVC (L).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 1 Inhalation before versus during airway clearance techniques

Outcome: 3 FVC (L)



Analysis 1.4. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 4 FVC (% pred).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 1 Inhalation before versus during airway clearance techniques

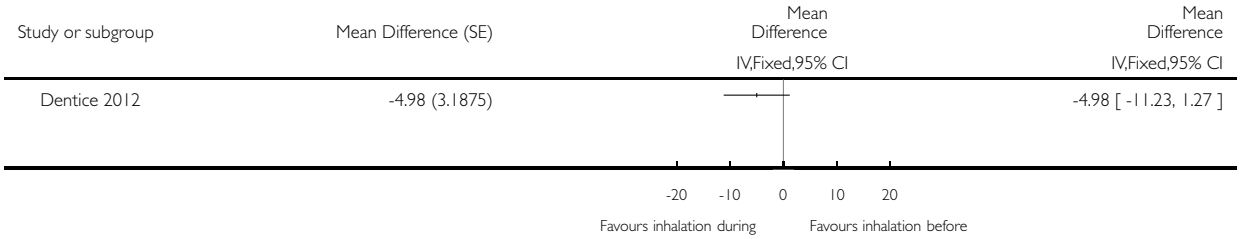
Outcome: 4 FVC (% pred)

Analysis 1.5. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 5 Perceived efficacy (mm).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 1 Inhalation before versus during airway clearance techniques

Outcome: 5 Perceived efficacy (mm)

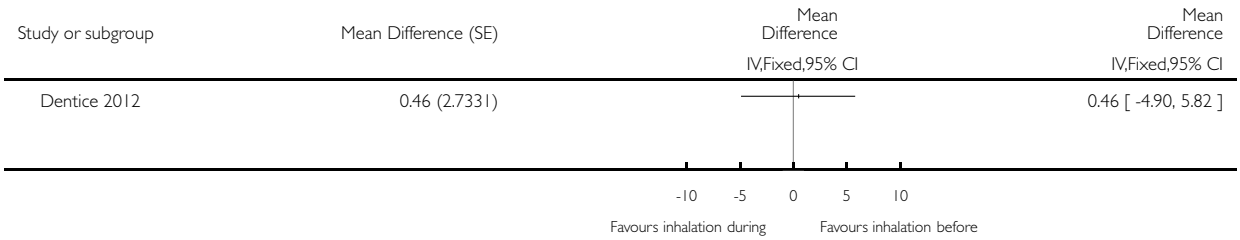


Analysis 1.6. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 6 Tolerability (mm).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 1 Inhalation before versus during airway clearance techniques

Outcome: 6 Tolerability (mm)

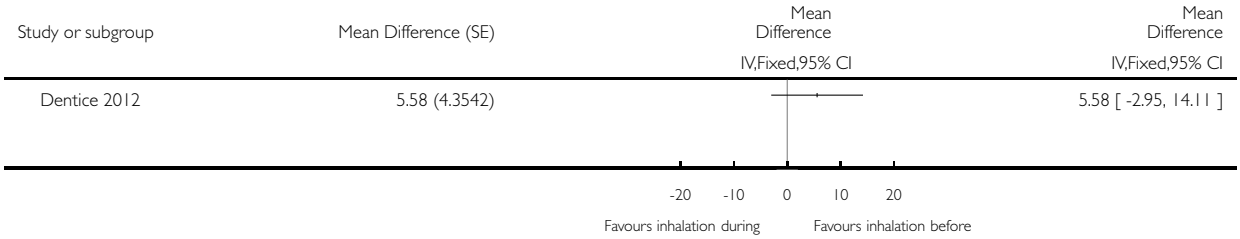


Analysis 1.7. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 7 Satisfaction (mm).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 1 Inhalation before versus during airway clearance techniques

Outcome: 7 Satisfaction (mm)

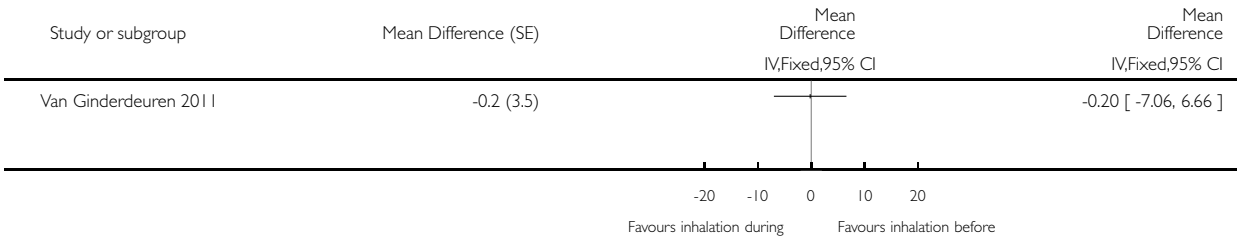


Analysis 1.8. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 8 Dyspnoea.

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 1 Inhalation before versus during airway clearance techniques

Outcome: 8 Dyspnoea

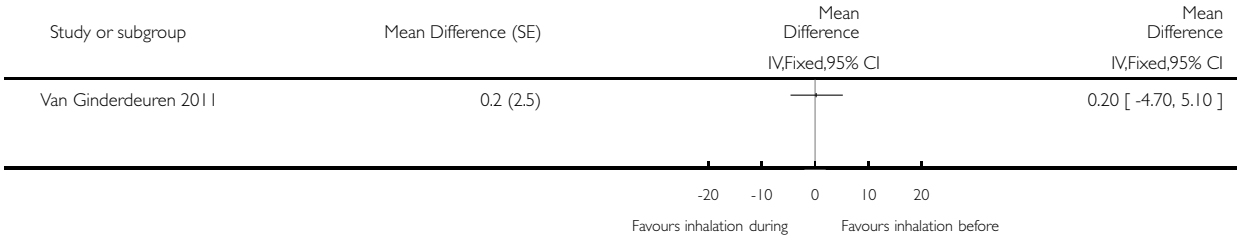


Analysis 1.9. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 9 Sputum wet weight.

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 1 Inhalation before versus during airway clearance techniques

Outcome: 9 Sputum wet weight

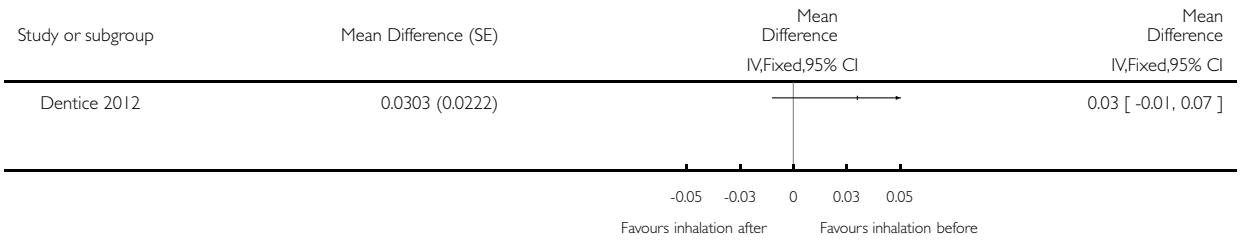


Analysis 2.1. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 1 FEV_1 (L).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 2 Inhalation before versus after airway clearance techniques

Outcome: 1 FEV_1 (L)

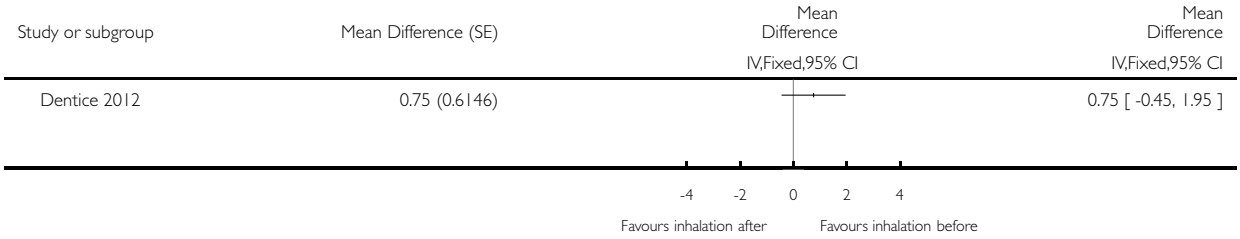


Analysis 2.2. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 2 FEV_1 (% pred).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 2 Inhalation before versus after airway clearance techniques

Outcome: 2 FEV_1 (% pred)

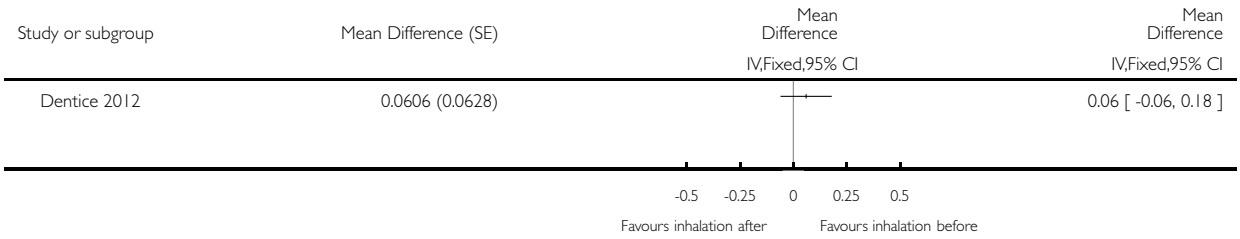


Analysis 2.3. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 3 FVC (L).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 2 Inhalation before versus after airway clearance techniques

Outcome: 3 FVC (L)

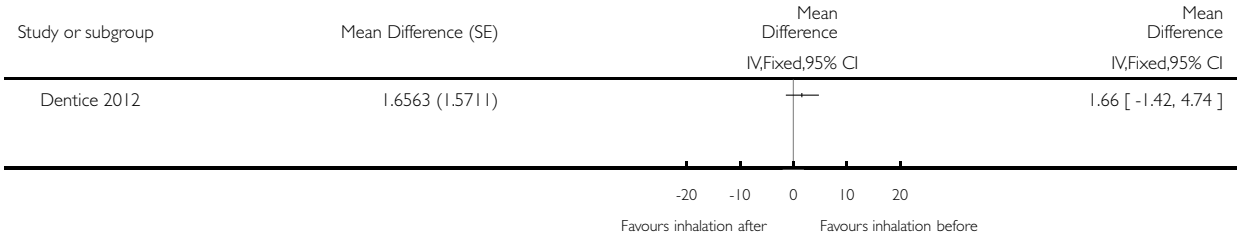


Analysis 2.4. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 4 FVC (% pred).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 2 Inhalation before versus after airway clearance techniques

Outcome: 4 FVC (% pred)

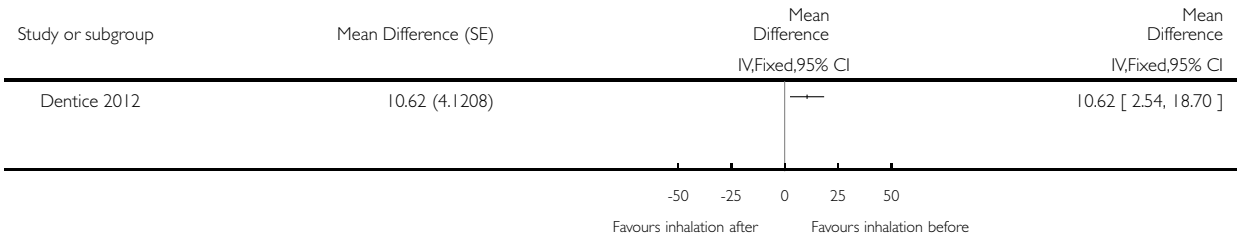


Analysis 2.5. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 5 Perceived efficacy (mm).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 2 Inhalation before versus after airway clearance techniques

Outcome: 5 Perceived efficacy (mm)

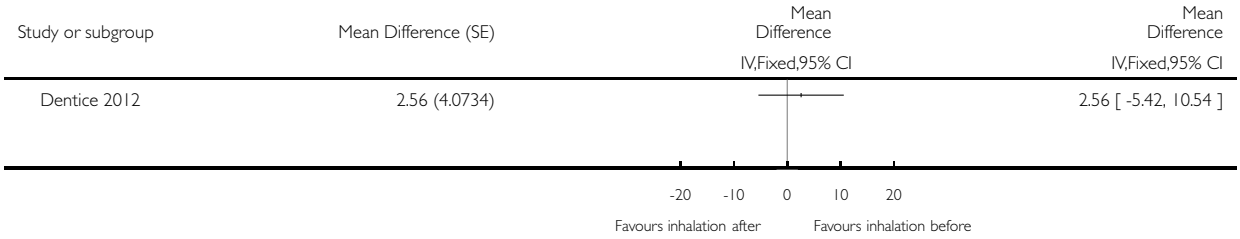


Analysis 2.6. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 6 Tolerability (mm).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 2 Inhalation before versus after airway clearance techniques

Outcome: 6 Tolerability (mm)

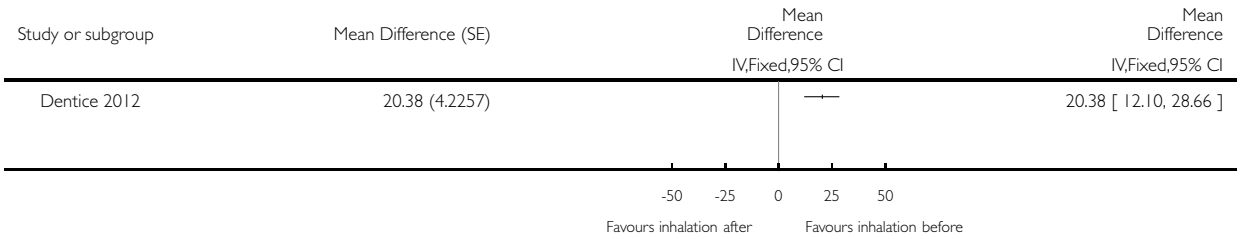


Analysis 2.7. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 7 Satisfaction (mm).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 2 Inhalation before versus after airway clearance techniques

Outcome: 7 Satisfaction (mm)

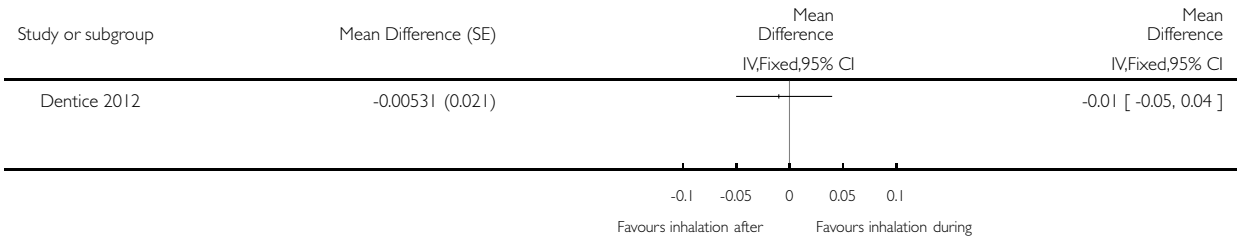


Analysis 3.1. Comparison 3 Inhalation during versus after airway clearance techniques, Outcome 1 FEV_1 (L).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 3 Inhalation during versus after airway clearance techniques

Outcome: 1 FEV_1 (L)

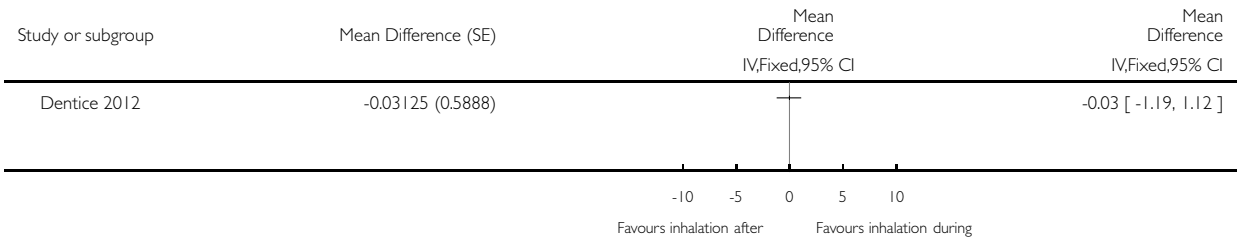


Analysis 3.2. Comparison 3 Inhalation during versus after airway clearance techniques, Outcome 2 FEV_1 (% pred).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 3 Inhalation during versus after airway clearance techniques

Outcome: 2 FEV_1 (% pred)

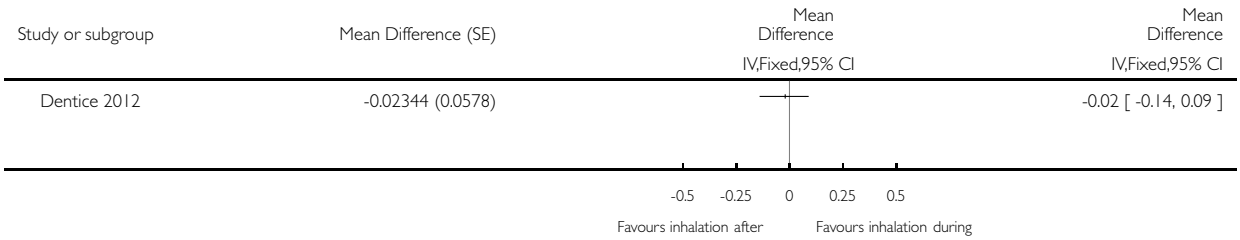


Analysis 3.3. Comparison 3 Inhalation during versus after airway clearance techniques, Outcome 3 FVC (L).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 3 Inhalation during versus after airway clearance techniques

Outcome: 3 FVC (L)

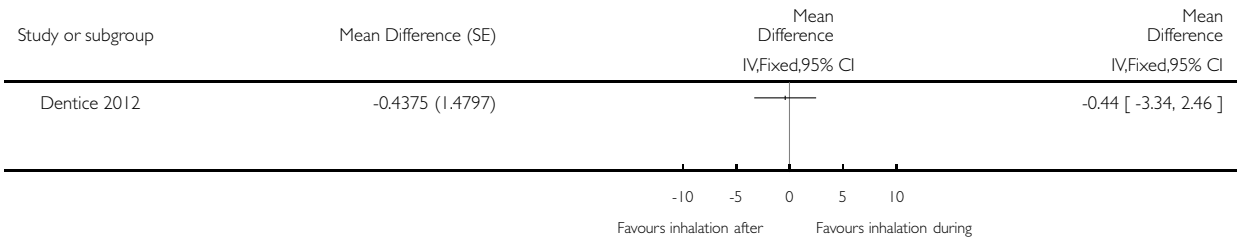


Analysis 3.4. Comparison 3 Inhalation during versus after airway clearance techniques, Outcome 4 FVC (% pred).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 3 Inhalation during versus after airway clearance techniques

Outcome: 4 FVC (% pred)

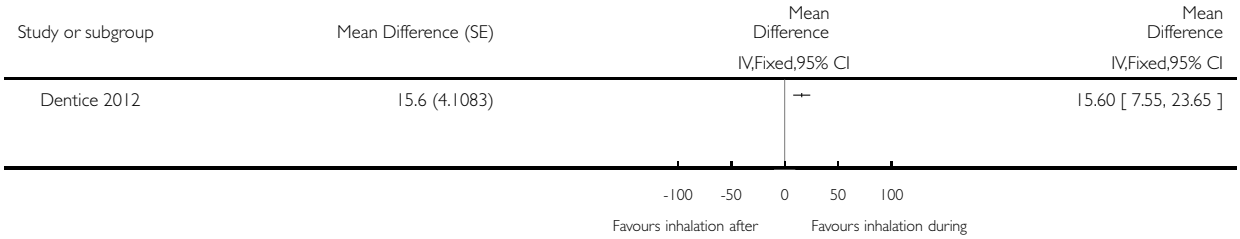


Analysis 3.5. Comparison 3 Inhalation during versus after airway clearance techniques, Outcome 5 Perceived efficacy (mm).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 3 Inhalation during versus after airway clearance techniques

Outcome: 5 Perceived efficacy (mm)

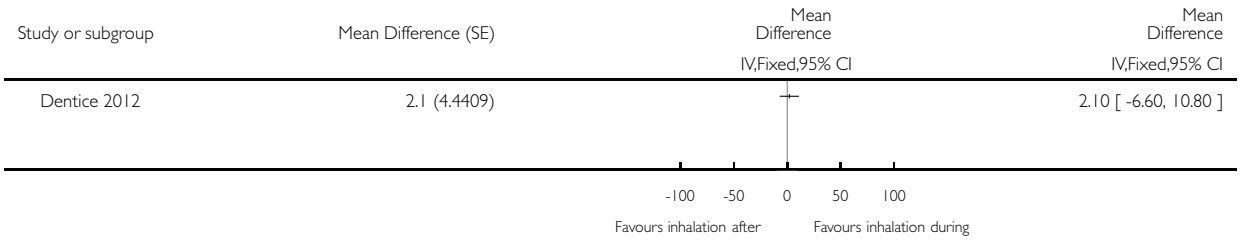


Analysis 3.6. Comparison 3 Inhalation during versus after airway clearance techniques, Outcome 6 Tolerability (mm).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 3 Inhalation during versus after airway clearance techniques

Outcome: 6 Tolerability (mm)

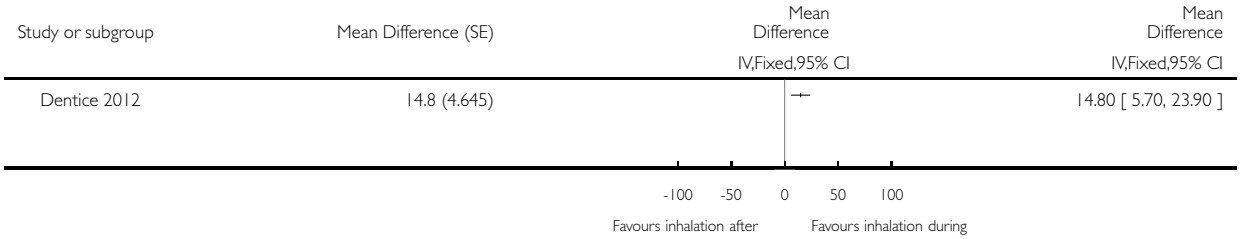


Analysis 3.7. Comparison 3 Inhalation during versus after airway clearance techniques, Outcome 7 Satisfaction (mm).

Review: Timing of hypertonic saline inhalation for cystic fibrosis

Comparison: 3 Inhalation during versus after airway clearance techniques

Outcome: 7 Satisfaction (mm)



APPENDICES

Appendix 1. PEDro search strategy

1. Hypertonic saline AND cystic fibrosis (via Simple Search interface)

Appendix 2. WHO Clinical Trial Register search strategy

1. Cystic fibrosis AND Hypertonic saline

WHAT'S NEW

Date	Event	Description
20 December 2016	New citation required and conclusions have changed	Previously there were no trials included in the review; however, for this update, two trials have been included (with a total of 63 participants) (Dentice 2012; Van Ginderdeuren 2011).
20 December 2016	New search has been performed	Changes have been made throughout the review. Two new trials have been included in the review (Dentice 2012; Van Ginderdeuren 2011).

CONTRIBUTIONS OF AUTHORS

RD and ME contributed to: the writing of the protocol; the conduct of the searches, the review of the search results; and the writing of the final review.

DECLARATIONS OF INTEREST

Both review authors are authors on the Dentice trial, therefore data extraction for this trial was also carried out at the editorial base (Dentice 2012).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

INDEX TERMS

Medical Subject Headings (MeSH)

*Mucociliary Clearance; Administration, Inhalation; Cystic Fibrosis [physiopathology; * therapy]; Drug Administration Schedule; Saline Solution, Hypertonic [*administration & dosage]; Sputum [metabolism]

MeSH check words

Female; Humans; Male