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Timing of hypertonic saline inhalation for cystic fibrosis (Review)
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[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. This is an update of a previously published Cochrane Review.

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: 28 February 2019.

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. The certainty of the evidence was assessed using GRADE.

Main results

The searches identified 104 trial reports which represented 51 trials, of which three cross-over trials (providing data on 77 participants) met our inclusion criteria. We present three comparisons: inhalation before versus during airway clearance techniques; inhalation before versus after airway clearance techniques; and inhalation during versus after airway clearance techniques. One trial (50 participants), given its three-arm design, was eligible for all three comparisons. No trials compared morning versus evening inhalation of hypertonic saline.

The evidence from the three trials was judged to be of low quality downgraded for limitations (high risk of bias due to blinding) and indirectness (all participants are adults, and therefore not applicable to children). Intervention periods ranged from one treatment to three

treatments in one day. There were no clinically important differences between the timing regimens of inhaling hypertonic saline before, during or after airway clearance techniques in the mean amount of improvement in lung function or symptom scores (77 participants), with the between-group comparisons being non-significant (low-certainty evidence). While there may be little or no difference in the rating of satisfaction when hypertonic saline was inhaled before versus during the airway clearance techniques (64 participants) (with the 95% confidence interval including the possibility of both a higher and lower rating of satisfaction), satisfaction may be lower on a 100-mm scale when inhaled after the airway clearance techniques compared to before: mean difference (MD) 20.38 mm (95% confidence interval (CI) 12.10 to 28.66) and when compared to during the techniques, MD 14.80 mm (95% CI 5.70 to 23.90). Perceived effectiveness showed similar results: little or no difference for inhalation before versus during airway clearance techniques (64 participants); may be lower when inhaled after the airway clearance techniques compared to before, MD 10.62 (95% CI 2.54 to 18.70); and also when compared to during the techniques, MD 15.60 (95% CI 7.55 to 23.65). There were no quality of life or adverse events reported in any of the trials.

Authors' conclusions

Timing of hypertonic saline inhalation makes little or no difference to lung function (low-certainty evidence). However, inhaling hypertonic saline before or during airway clearance techniques may maximise perceived efficacy and satisfaction. The long-term efficacy of hypertonic saline has only been established for twice-daily inhalations; 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.

The identified 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.

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. This is an update of a previously published Cochrane Review.

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: 28 February 2019.

Study characteristics

The review included three studies with 77 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. All 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 may be more effective and satisfying than inhaling hypertonic saline after airway clearance. No studies comparing morning and evening inhalation were found. The long-term efficacy of hypertonic saline has only been established for twice-daily inhalations; 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 low. 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.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Inhalation before compared with during airway clearance techniques for cystic fibrosis

Inhalation before compared with during airway clearance techniques for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: inhalation before airway clearance techniques

Comparison: inhalation during airway clearance techniques

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Inhalation during airway clearance techniques	Inhalation before airway clearance techniques				
FEV₁ % predicted Follow-up: before treatment to ~2 hours later	Not reported ¹	The mean FEV ₁ (% predicted) was 0.56% higher (0.48% lower to 1.60% higher) in the inhalation before airway clearance techniques.	NA	63 (2 studies)	⊕⊕⊕⊕ low^{2,3}	FEV ₁ (L) also showed no statistically significant difference between groups. Participants received both inhalation approaches as cross-over design.
FVC % predicted Follow-up: before treatment to 2 hours later	Not reported ¹	The mean FVC (% predicted) was 2.09% higher (0.08% higher to 4.11% higher) in the inhalation before airway clearance techniques.	NA	50 (1 study)	⊕⊕⊕⊕ low^{2,3}	FEV ₁ (L) showed no statistically significant difference between groups. Participants received both inhalation approaches as cross-over design.
QoL	Outcome not reported.		NA	NA	NA	
Symptom scores	See comments.		NA	76 (3 studies)	⊕⊕⊕⊕ low^{2,3}	All of the symptom scores suggest no statistically significant difference between the groups. This outcome includes a range of symptom scores from many different studies

						but number of participants contributing to each symptom score varies.
Measures of sputum clearance: sputum wet weight immediately (g)	Not reported ¹	The mean wet weight of sputum during the application of the intervention was 0.26 g lower (4.79 g lower to 4.27 g higher) in the inhalation before airway clearance techniques.	NA	26 (2 studies)	⊕⊕⊕⊕ low^{2,3}	The mean wet weight of sputum for the 24 hours following treatment suggests no statistically significant difference between the groups. Participants received both inhalation approaches as cross-over design.
LCI Follow-up: 90 minutes later	Not reported ¹	The mean LCI was 0.02 lower (0.63 lower to 0.59 higher) in the inhalation before airway clearance techniques.	NA	13 (1 study)	⊕⊕⊕⊕ low^{2,3}	The mean LCI immediately after treatment suggests no statistically significant difference between the groups. Participants received both inhalation approaches as cross-over design.
Adverse events	Outcome not reported.		NA	NA	NA	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FEV₁:** forced expiratory volume at 1 second; **FVC:** forced vital capacity; **LCI:** lung clearance index; **MD:** mean difference; **QoL:** quality of life

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

1. Only differences between inhalation before and during airway clearance techniques were presented, results within the inhalation during airway clearance techniques were not presented therefore an assumed risk cannot be calculated.

2. Downgraded once due to high risk due to lack of blinding of participants and personnel.

3. Downgraded once for lack of applicability as studies included only adults so results are not applicable to children.

Summary of findings 2. Inhalation before compared with after airway clearance techniques for cystic fibrosis

Inhalation before compared with after airway clearance techniques for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: inhalation before airway clearance techniques

Comparison: inhalation after airway clearance techniques

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Inhalation after airway clearance techniques	Inhalation before airway clearance techniques				
FEV₁ % predicted Follow-up: before treatment to 2 hours later	Not reported ¹	The mean FEV ₁ (% predicted) was 0.75% higher (0.45% lower to 1.95% higher) in the inhalation before airway clearance techniques.	NA	50 (1 study)	⊕⊕⊕⊕ low^{2,3}	FEV ₁ (L) also showed no statistically significant difference between groups. Participants received both inhalation approaches as cross-over design.
FVC % predicted Follow-up: before treatment to 2 hours later	Not reported ¹	The mean FVC (% predicted) was 1.66% higher (1.42% lower to 4.74% higher) in the inhalation before airway clearance techniques.	NA	50 (1 study)	⊕⊕⊕⊕ low^{2,3}	FVC (L) showed no statistically significant difference between groups. Participants received both inhalation approaches as cross-over design.
QoL	Outcome not reported.		NA	NA	NA	
Symptom scores	See comments.		NA	50 (1 study)	⊕⊕⊕⊕ low^{2,3}	Three symptom scores have been presented: Perceived efficacy shows a statistically significant difference in favour of inhalation before airway clearance techniques (MD 10.62; 95% CI 2.54 to 18.70) Tolerability showed no statistically significant difference between groups. Satisfaction shows a statistically significant difference in favour of inhalation before airway clearance techniques, MD 20.38 (95% CI 12.10 to 28.66)
Measures of sputum clearance	Outcome not reported.		NA	NA	NA	

LCI	Outcome not reported	NA	NA	NA
Adverse events	Outcome not reported	NA	NA	NA

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FEV₁:** forced expiratory volume at 1 second; **FVC:** forced vital capacity; **LCI:** lung clearance index; **MD:** mean difference; **QoL:** quality of life

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

1. Only differences between inhalation before and during airway clearance techniques were presented, results within the inhalation during airway clearance techniques were not presented therefore an assumed risk cannot be calculated.
2. Downgraded once due to high risk due to lack of blinding of participants and personnel.
3. Downgraded once for lack of applicability as studies included only adults so results are not applicable to children.

Summary of findings 3. Inhalation during compared with after airway clearance techniques for cystic fibrosis

Inhalation during compared with after airway clearance techniques for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: inhalation during airway clearance techniques

Comparison: Inhalation after airway clearance techniques

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Inhalation after airway clearance techniques	Inhalation during airway clearance techniques				
FEV₁ % predicted	Not reported ¹	The mean FEV ₁ (% predicted) was 0.03% lower (1.19% lower to 1.12%	NA	50 (1 study)	⊕⊕⊕⊕ low ^{2,3}	FEV ₁ (L) also showed no statistically significant difference between groups.

Follow-up: before treatment to 2 hours later		higher) in the inhalation during airway clearance techniques.				Participants received both inhalation approaches as cross-over design.
FVC % predicted	Not reported ¹	The mean FVC (% predicted) was 0.44% lower (3.34% lower to 2.46% higher) in the inhalation during airway clearance techniques.	NA	50 (1 study)	⊕⊕⊕⊕ low^{2,3}	FVC (L) also showed no statistically significant difference between groups. Participants received both inhalation approaches as cross-over design.
Follow-up: before treatment to 2 hours later						
QoL	Outcome not reported.		NA	NA	NA	
Symptom scores	See comments.		NA	50 (1 study)	⊕⊕⊕⊕ low^{2,3}	Three symptom scores have been presented: Perceived efficacy shows a statistically significant difference in favour of inhalation during airway clearance techniques, MD 15.60 (95% CI 7.55 to 23.65) Tolerability showed no statistically significant difference between groups. Satisfaction shows a statistically significant difference in favour of inhalation during airway clearance techniques, MD 14.80 (95% CI 5.70 to 23.90)
Measures of sputum clearance	Outcome not reported.		NA	NA	NA	
LCI	Outcome not reported.		NA	NA	NA	
Adverse events	Outcome not reported.		NA	NA	NA	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FEV₁:** forced expiratory volume at 1 second; **FVC:** forced vital capacity; **LCI:** lung clearance index; **MD:** Mean difference; **QoL:** quality of life

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

1. Only differences between inhalation before and during airway clearance techniques were presented, results within the inhalation during airway clearance techniques were not presented therefore an assumed risk cannot be calculated.
2. Downgraded once due to high risk due to lack of blinding of participants and personnel.
3. Downgraded once for lack of applicability as studies included only adults so results are not applicable to children.

BACKGROUND

Description of the condition

Cystic 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 2018). 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 (QoL), 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 (FEV₁) were demonstrated over two to four weeks of therapy and QoL and pulmonary exacerbation rates were improved compared to placebo interventions over 48 weeks of treatment (Wark 2018).

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 any timing regimen 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.

This is an update of a previously published Cochrane Review (Elkins 2012; Elkins 2016).

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.
 - a. forced expiratory volume at one second (FEV₁)
 - b. forced vital capacity (FVC)
2. Patient-reported outcomes, using validated scales or subjective reporting measures
 - a. measures of QoL
 - b. 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
 - a. forced expiratory flow between 25% and 75% of the vital capacity (FEF₂₅₋₇₅)
 - b. maximal instantaneous forced flow when 25% of the FVC remains to be exhaled (MEF₂₅)
 - c. total lung capacity (TLC)
 - d. residual volume (RV)
 - e. functional residual capacity (FRC)
 - f. 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)
 - a. admission rates to hospital (defined as either number of inpatient hospital admissions or days as a hospital inpatient)
 - b. courses of IV antibiotics (whether received in hospital or in the home)
 - c. 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

A comprehensive search strategy was formulated in an attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

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: 28 February 2019.

In addition, we searched the [Physiotherapy Evidence Database \(PEDro\)](#) ([Michaleff 2011](#)) and the [WHO International Clinical Trials Registry Platform](#) for all years available ([Appendix 1](#); [Appendix 2](#)). Date of last search: 21 February 2019.

Searching other resources

We hand-searched the biennial Australia and New Zealand CF Conference Proceedings from 1995 to 2017.

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). Additional data were sought from the authors of the O'Neill trial (O'Neill 2016) and data were received for all requested outcomes.

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.

Summary of findings tables

In a post hoc change, we have presented three summary of findings tables, one for each comparison (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). We have included the following outcomes: FEV₁, FVC, measures of QoL, symptom scores, measures of sputum clearance, lung clearance index and adverse events.

We determined the certainty of the evidence using the GRADE approach; and downgraded evidence in the presence of: a high risk of bias in at least one study; indirectness of the evidence; unexplained heterogeneity or inconsistency; imprecision of results, or a high probability of publication bias. We downgraded evidence by one level if we considered the limitation to be serious and by two levels if very serious.

RESULTS

Description of studies

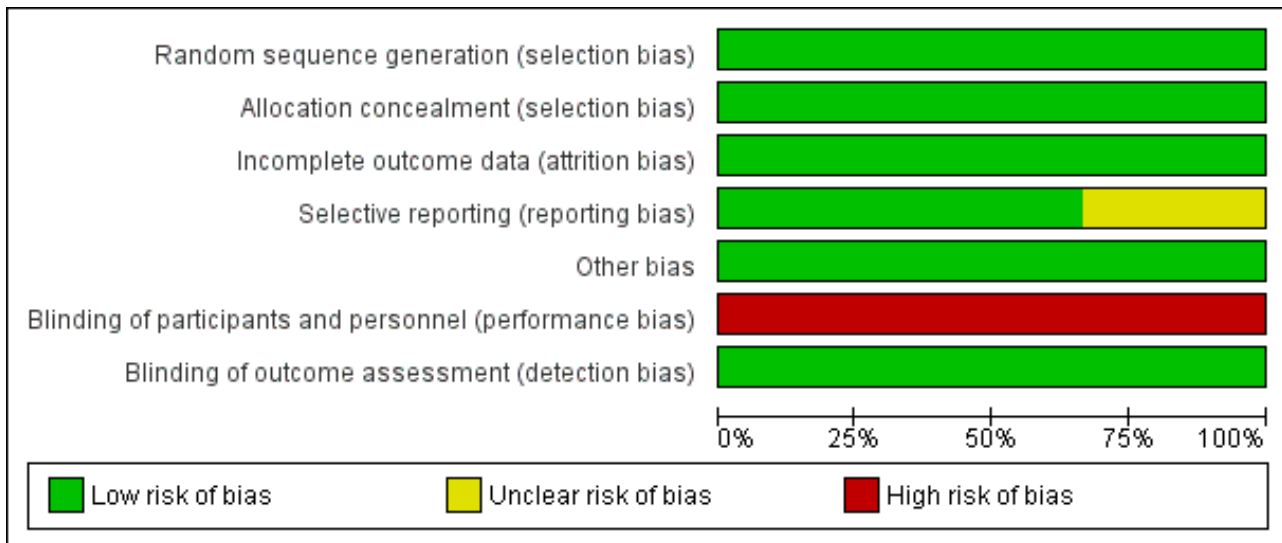
Results of the search

The searches identified 104 trial reports which represented 50 trials.

Included studies

Three trials were eligible for inclusion, which provided data for a total of 77 participants (Dentice 2012; Van Ginderdeuren 2011; O'Neill 2016) (Figure 1). One trial has not yet been published in full but has been presented as an oral presentation at a conference (although additional data has been provided by the trial authors) (Van Ginderdeuren 2011). No trial was identified regarding timing of hypertonic saline inhalation in relation to time of day.

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



Trial characteristics

The three included studies were randomised, cross-over trials with concealed allocation, intention to treat analysis and blinded assessors (Dentice 2012; Van Ginderdeuren 2011; O'Neill 2016). 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. The third trial also delivered a single treatment on each trial day, but only two timing regimens (inhalation before airway clearance techniques and inhalation during airway clearance techniques) were compared, so there were only two trial days (O'Neill 2016).

Participants

Clarification of participant data was requested from the authors of the two of the three 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 FEV₁ 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; had received a lung transplant; were colonised with *Burkholderia cepacia* complex; were not clinically stable; had experienced haemoptysis greater than 60 mL within the last month; or were thrombocytopenic or pregnant. 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. The third study recruited 14 adults (mean (SD) age 33

(12) years), who were nearing the end of a course of intravenous antibiotics (days 10 to 14) for a pulmonary exacerbation of cystic fibrosis (O'Neill 2016). Eligibility criteria included being productive of at least 10 g of sputum daily and demonstrated tolerance of hypertonic (7%) saline through either past or current use. The participants' mean (SD) FEV₁ was 51 (22) per cent predicted.

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 third trial (O'Neill 2016) administered 4mL of 7% hypertonic saline via a Portex updraft nebuliser (Smiths Medical, UK). Airway clearance involved 10 supervised cycles of oscillating PEP using the Acapella Duet device with forced expiration techniques, which in total required about 20 minutes. When hypertonic saline was allocated to be administered during airway clearance, this was achieved by attaching the updraft nebuliser to the Acapella Duet. On both days, 200 micrograms of salbutamol was administered 15 minutes before the commencement of the randomly allocation intervention for that day. The use of co-interventions (such as bronchodilators and other inhaled medications) was not reported in the other two studies (Dentice 2012; Van Ginderdeuren 2011).

Outcomes measures

One trial measured the change in FEV₁ 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).

The third trial reported FEV₁ and FEF₂₅₋₇₅ as a percentage of the predicted value (O'Neill 2016). Ease of use of the intervention and satisfaction with the intervention were also rated by the participants and the treating physiotherapists on a 100-mm visual analogue scale. The wet weight of sputum produced and the number of coughs occurring during the allocated treatment session were also recorded, as was the wet weight of sputum during the

subsequent 24 hours. Using a multiple breath washout test, the LCI and FRC were also recorded before, immediately after, and 90 minutes after each allocated treatment regimen. The duration of treatment was also noted.

Excluded studies

Of the remaining 46 studies identified through our search strategy, two were excluded because they did not involve the administration of hypertonic saline at all and one because the comparison of timing regimens was confounded by the use of different airway clearance techniques in the two arms of the study. A further 43 studies were excluded because the interventions they compared did not differ in the timing of hypertonic saline inhalation (Excluded studies).

Risk of bias in included studies

Please refer to [Figure 1](#); [Figure 2](#).

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
Dentice 2012							
O'Neill 2016							
Van Ginderdeuren 2011							

Allocation

Generation of sequence

All three trials reported adequate methods of random generation of the allocation sequence: computer-generated list (Dentice 2012; O'Neill 2016) and allocations drawn from a box that had been

shaken (Van Ginderdeuren 2011). Thus, the overall risk of bias for all trials due to the method of generation of the random sequence was low.

Concealment of allocation

Two trials reported using sealed opaque envelopes (Dentice 2012; Van Ginderdeuren 2011) and one reported using an independent investigator to conceal the allocation list (O'Neill 2016), so the overall risk of bias for all trials due to the non-concealment of allocation was low.

Blinding

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

Incomplete outcome data

All trials reported all available data. One trial stated no withdrawals occurred (Dentice 2012). The second trial 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%). The third trial ceased recruitment at 14 participants instead of the intended 31 because an interim analysis showed that the treatment was unlikely to be statistically or clinically significant (O'Neill 2016). Additionally, one of the 14 participants withdrew and data were reported on the remaining 13 participants (93%). Therefore, the risk of bias due to attrition was low across all trials.

Selective reporting

Two trials had a low risk of bias for this domain; one trial was prospectively registered and remained consistent with this protocol (Dentice 2012); one trial was prospectively registered and reported all of the registered outcome measures, but some additional unregistered outcome measures (ease, satisfaction, cough and treatment duration) were also reported (O'Neill 2016). The third trial was not registered and therefore had an unclear risk of bias (Van Ginderdeuren 2011).

Other potential sources of bias

No other potential sources of bias were identified.

All 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

See: [Summary of findings for the main comparison Inhalation before compared with during airway clearance techniques for cystic fibrosis](#); [Summary of findings 2 Inhalation before compared with after airway clearance techniques for cystic fibrosis](#); [Summary of findings 3 Inhalation during compared with after airway clearance techniques for cystic fibrosis](#)

Inhalation before versus during airway clearance techniques

Three studies with a total of 77 participants contributed data to this comparison (Dentice 2012; Van Ginderdeuren 2011; O'Neill 2016).

Primary outcomes

1. Lung function

a. FEV₁

One trial (50 participants) provided data in litres for this outcome (Dentice 2012). The change in FEV₁ from immediately before a treatment to two hours later was higher on average when hypertonic saline was inhaled before airway clearance techniques, but this was not statistically significant (Analysis 1.1). Two trials (63 participants) reported estimates of the effect on FEV₁ using % predicted data, however, this difference was not statistically significant (low-certainty evidence) (Analysis 1.2) (Dentice 2012; O'Neill 2016).

b. FVC

One trial (50 participants) 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) (low-certainty evidence) (Analysis 1.4).

2. Patient-reported outcomes

a. QoL

No trial reported this outcome.

b. Symptom scores

Three studies with a total of 77 participants contributed data to this comparison (low-certainty evidence) (Dentice 2012; O'Neill 2016; Van Ginderdeuren 2011).

Cough in the 24 hours following treatment was reported for 13 participants in one trial (O'Neill 2016). There was no significant difference between the groups in the number of coughs (Analysis 1.5).

The remaining symptoms were all measured on a 100-mm visual analogue scale.

Dyspnoea was reported for 12 participants in one trial (Van Ginderdeuren 2011). There was no significant difference in the severity of dyspnoea between the groups (Analysis 1.6).

Tolerability and perceived efficacy were reported for 50 participants in one trial (Dentice 2012), there were no significant differences between the groups for either outcome (Analysis 1.7; Analysis 1.8).

Ease of sputum clearance was reported for 13 participants in one trial (O'Neill 2016). The same trial also reported data estimates of ease of sputum clearance from the treating physiotherapist. There were no significant between-group differences for the patient ratings (Analysis 1.9), nor for the therapist ratings (Analysis 1.10).

Satisfaction with the treatment regimen was rated by the patients in two trials (64 participants) (Dentice 2012; O'Neill 2016). The pooled result of meta-analysis indicated no significant difference between the groups (Analysis 1.11). The O'Neill trial also obtained data on satisfaction from the treating physiotherapist (O'Neill

2016). Again there was no significant difference between the groups (Analysis 1.12).

Secondary outcomes

1. Measures of sputum clearance

Two trials provided data from 25 participants for wet weight of sputum during the application of the intervention (O'Neill 2016; Van Ginderdeuren 2011). The pooled result of meta-analysis indicated no significant difference between the groups (low-certainty evidence) (Analysis 1.13). One of the trials also collected data on wet weight of sputum for the 24 hours following treatment, again there was no significant difference between the groups (O'Neill 2016) (Analysis 1.14).

2. Measures of exercise capacity

None of the trials reported on this outcome.

3. Mortality

No trial reported this outcome.

4. Other pulmonary parameters

a. FEF₂₅₋₇₅

One trial provided FEF₂₅₋₇₅ data as % predicted for 13 participants (O'Neill 2016) There was no significant difference between the groups (Analysis 1.15).

e. FRC

One trial (13 participants) provided data on FRC immediately after the treatment and 90 minutes later (O'Neill 2016). There was no significant difference between the groups immediately after the treatment (Analysis 1.16) or at 90 minutes (Analysis 1.17).

f. LCI

One trial provided data on LCI immediately after the treatment and 90 minutes later (O'Neill 2016). There was no significant difference between the groups immediately after the treatment (Analysis 1.18) or at 90 minutes (low-certainty evidence) (Analysis 1.19).

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 all trials (Dentice 2012; O'Neill 2016; Van Ginderdeuren 2011).

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

There were no adverse events in any trial (Dentice 2012; Van Ginderdeuren 2011; O'Neill 2016).

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. FEV₁

The change in FEV₁ 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 (low-certainty evidence) (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 (low-certainty evidence) (Analysis 2.4).

2. Patient-reported outcomes

a. QoL

The trial did not report 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) (low-certainty evidence) (Analysis 2.5)

Tolerability was not rated significantly differently when hypertonic saline was inhaled before versus after airway clearance techniques (low-certainty evidence) (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) (low-certainty evidence) (Analysis 2.7).

Secondary outcomes

1. Measures of sputum clearance

The trial did not report this outcome.

2. Measures of exercise capacity

The trial did not report this outcome.

3. Mortality

The trial did not report this outcome.

4. Other pulmonary parameters

The trial did not report this outcome.

5. Frequency of exacerbations of respiratory infection

The trial did not report 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. FEV₁

The change in FEV₁ 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 (low-certainty evidence) ([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 (low-certainty evidence) ([Analysis 3.3](#)) or % predicted ([Analysis 3.4](#)).

2. Patient-reported outcomes

a. QoL

The trial did not report 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) (low-certainty evidence) ([Analysis 3.5](#)).

Tolerability was not rated significantly differently when hypertonic saline was inhaled during versus after airway clearance techniques (low-certainty evidence) ([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 5.70 to 23.90) (low-certainty evidence) ([Analysis 3.7](#)).

Secondary outcomes

1. Measures of sputum clearance

The trial did not report this outcome.

2. Measures of exercise capacity

The trial did not report this outcome.

3. Mortality

The trial did not report this outcome.

4. Other pulmonary parameters

The trial did not report this outcome.

5. Frequency of exacerbations of respiratory infection

The trial did not report 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 51 studies, of which three studies were eligible for inclusion - providing data for 77 participants. All 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 two trials provided a single treatment for each arm of the trial on separate days ([Van Ginderdeuren 2011](#); [O'Neill 2016](#)).

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](#); [O'Neill 2016](#)).

There were little or no differences in symptom scores when the timing regimens of before or during airway clearance techniques were compared. Outcomes included cough, dyspnoea, tolerability, ease of clearance and overall satisfaction ([Dentice 2012](#); [O'Neill 2016](#); [Van Ginderdeuren 2011](#)). Ease of sputum clearance and overall satisfaction were also estimated by the treating physiotherapist in one trial, but there were little or no differences between the timing regimens ([O'Neill 2016](#)).

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](#)). Satisfaction with the entire treatment regimen may be lower when hypertonic saline was inhaled after physical airway clearance techniques, as opposed to before or during the techniques ([Dentice 2012](#)).

Additional outcomes for the before versus during timing comparison, which included wet weight of sputum (during and 24 hours following), FEF₂₅₋₇₅, FRC (immediately and 90 minutes post), LCI (immediately and 90 minutes post), showed there may be little or no difference between these timing regimens ([Dentice 2012](#); [O'Neill 2016](#); [Van Ginderdeuren 2011](#)).

One trial achieved delivery of hypertonic saline during airway clearance by using an Acapella duet device, which combines a nebuliser in series with an oscillating PEP mechanism ([O'Neill 2016](#)). Devices such as this may introduce additional considerations. For example, the Acapella duet device substantially reduces the duration of treatment ([O'Neill 2016](#)), but it also substantially reduces the dose received by the patient ([Berlinski 2014](#)). These other issues were not included in the outcome

measures of this systematic review, but clinicians should nevertheless consider these issues when deciding whether to use such a device to deliver hypertonic saline during airway clearance.

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

The evidence for each outcome was rated as low according to the GRADE system, indicating that further research is very likely to have an important impact on our confidence in the estimates of effect and is likely to change the estimates. The GRADE result reflects two limitations of the included studies. The first issue is poor applicability, because studies included only adults so results are not applicable to children. The other issue is the lack of blinding. While it is often difficult for trials of physical interventions to achieve blinding, this was achieved in most of the trials in the Cochrane Review of timing of dornase alpha (Dentice 2018) using a double-dummy method. It is disappointing that none of the included trials in the present review used this method to achieve blinding.

Agreements and disagreements with other studies or reviews

This 2019 review update identified an additional trial (O'Neill 2016), which shared outcome measures with the previous two eligible trials, permitting meta-analysis for the before versus during timing comparison. 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 included trials 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, lung clearance index, functional residual capacity, sputum wet weight, dyspnoea or cough after a single treatment session. However, participants may be 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 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 three 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 (FEV₁) 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 trial), and equated to approximately 1% of the predicted normal value (Dentice 2012). Therefore, although the mean results favoured inhalation of hypertonic saline before physical airway clearance techniques, any effects of the timing regimens on FEV₁ are probably too small to be clinically important. However, unlike the narrow confidence intervals seen in the FEV₁ 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.

Devices that combine nebulisation with (oscillating) PEP have the potential to improve adherence to therapy because they may substantially reduce the overall treatment duration (O'Neill 2016). However, a benchtop study has demonstrated that the delivered dose decreases by 84% when delivered via the Acapella Duet

(Berlinski 2014), presumably due to obstruction of the aerosol pathway. Several studies suggest that when 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 2006b). These issues warrant further investigation so that an informed recommendation can be made regarding nebulisers that incorporate PEP or oscillating PEP mechanisms that obstruct the aerosol pathway.

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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

Timing of hypertonic saline inhalation for cystic fibrosis (Review)

Dentice 2012 (Continued)

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.
Selective reporting (reporting bias)	Low risk	Consistent with the prospectively registered trial protocol.
Other bias	Low risk	None identified.
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.

O'Neill 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)).

Timing of hypertonic saline inhalation for cystic fibrosis (Review)

O'Neill 2016 (Continued)

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	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	Randomisation was electronically generated.
Allocation concealment (selection bias)	Low risk	The random allocation list was concealed by an administrator independent of the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant was lost to follow-up.
Selective reporting (reporting bias)	Low risk	Consistent with the prospectively registered trial protocol.
Other bias	Low risk	None identified.
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.

Timing of hypertonic saline inhalation for cystic fibrosis (Review)

Van Ginderdeuren 2011 (Continued)

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
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	None identified.
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.

FEV₁: 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.

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Study	Reason for exclusion
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.
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.
Corcoran 2017	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	Different airway clearance techniques in the two study arms confound the comparison of the effects of timing.
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.

Study	Reason for exclusion
Mainz 2015	Intervention not related to the timing of hypertonic saline inhalation.
Nenna 2017	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.
Stahl 2017	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.

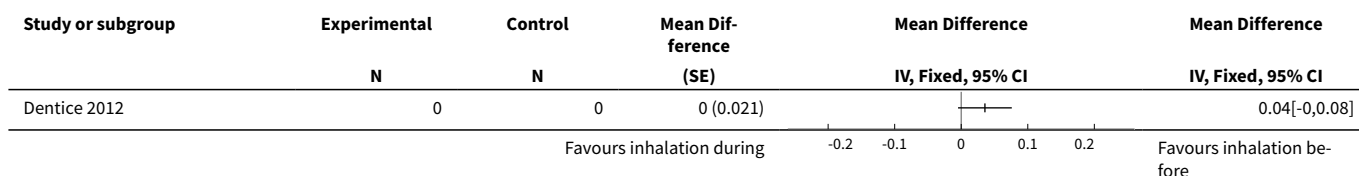
DATA AND ANALYSES

Comparison 1. Inhalation before versus during airway clearance techniques

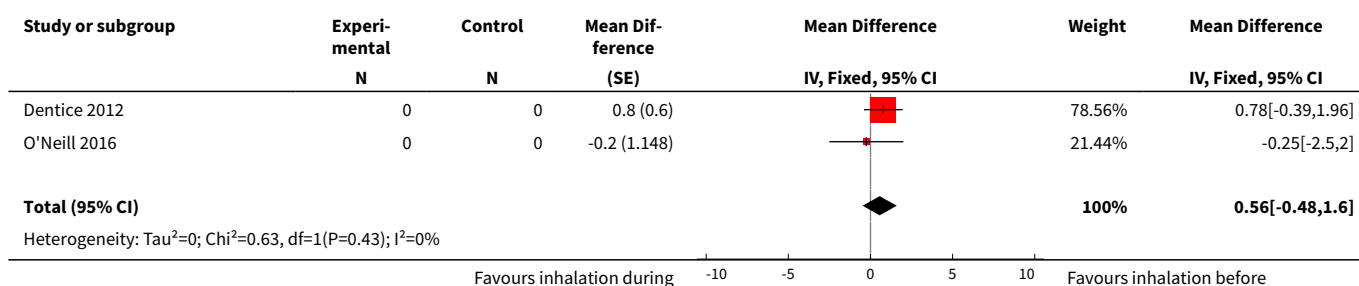
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV ₁ (L)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
2 FEV ₁ (% pred)	2		Mean Difference (Fixed, 95% CI)	0.56 [-0.48, 1.60]
3 FVC (L)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
4 FVC (% pred)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
5 Coughs (n)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
6 Dyspnoea (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
7 Tolerability (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected

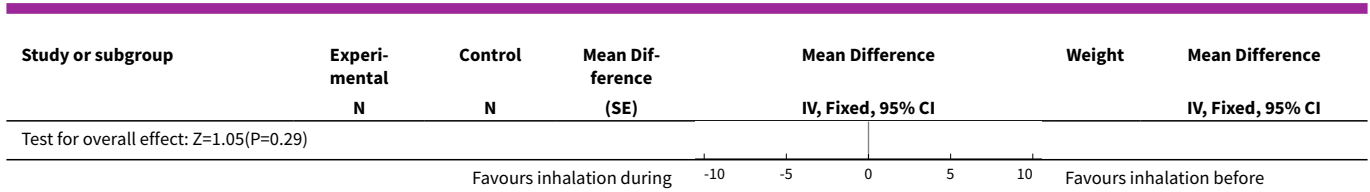
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Perceived efficacy (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
9 Ease (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
10 Ease rated by therapist (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
11 Satisfaction (mm)	2		Mean Difference (Fixed, 95% CI)	4.91 [-1.58, 11.41]
12 Satisfaction rated by therapist (mm)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
13 Sputum wet weight immediately (g)	2		Mean Difference (Fixed, 95% CI)	-0.26 [-4.79, 4.27]
14 Sputum wet weight next 24 hours (g)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
15 FEF ₂₅₋₇₅ (% pred)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
16 FRC immediately (L)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
17 FRC at 90 min (L)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
18 LCI immediately	1		Mean Difference (Fixed, 95% CI)	Totals not selected
19 LCI at 90 min	1		Mean Difference (Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 1 FEV₁ (L).

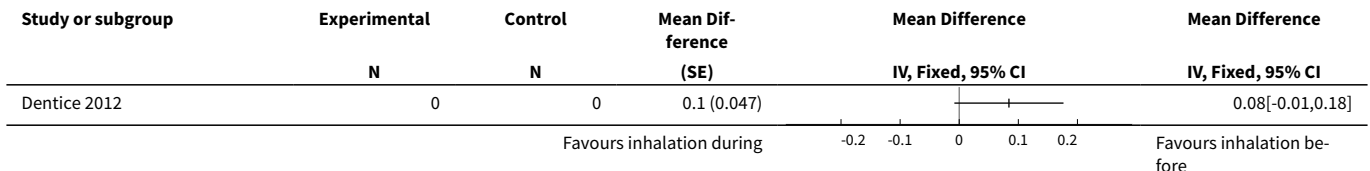


Analysis 1.2. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 2 FEV₁ (% pred).

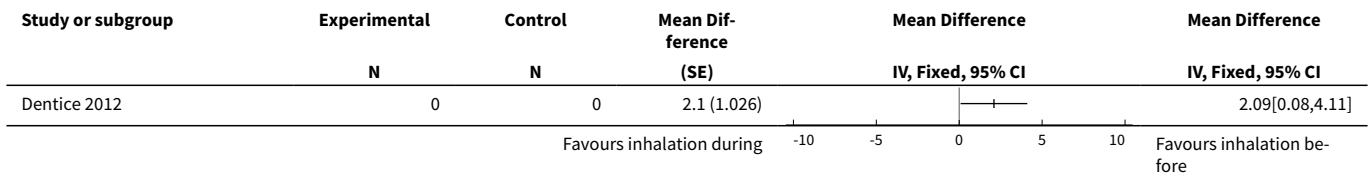




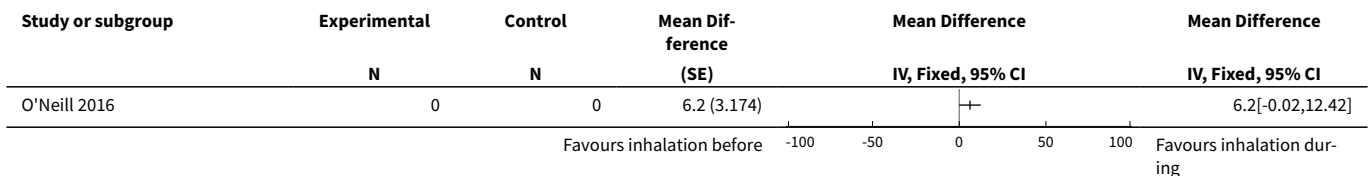
Analysis 1.3. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 3 FVC (L).



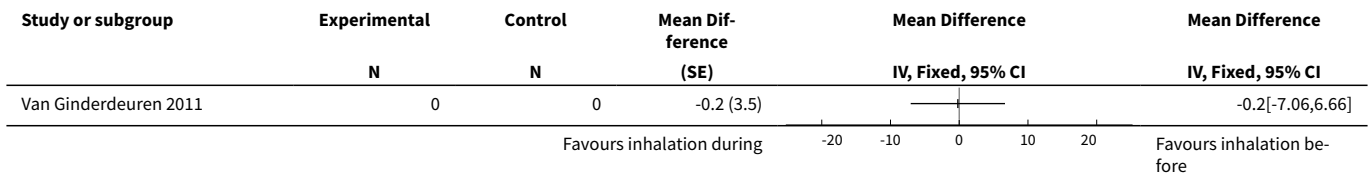
Analysis 1.4. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 4 FVC (% pred).



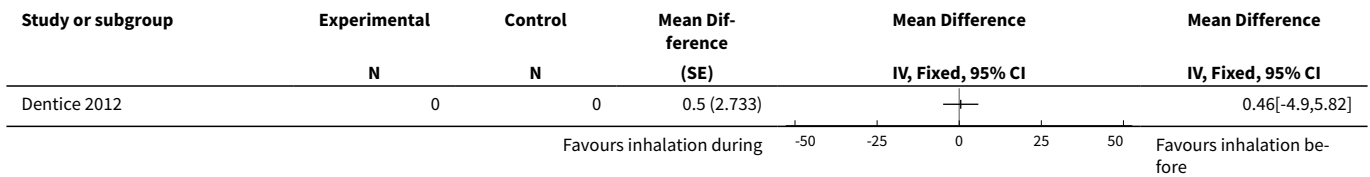
Analysis 1.5. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 5 Coughs (n).



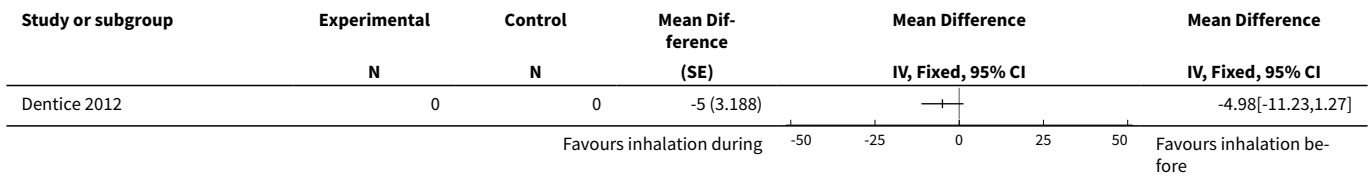
Analysis 1.6. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 6 Dyspnoea (mm).



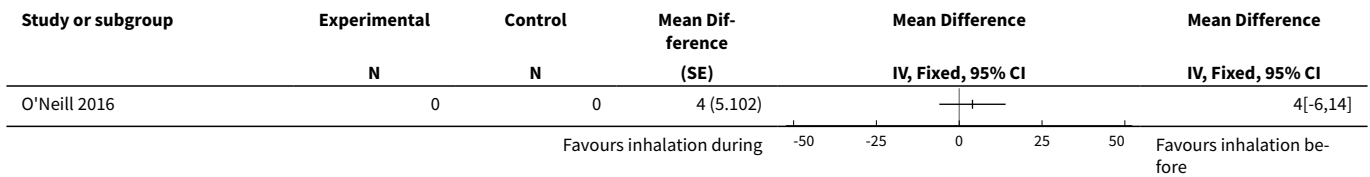
Analysis 1.7. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 7 Tolerability (mm).



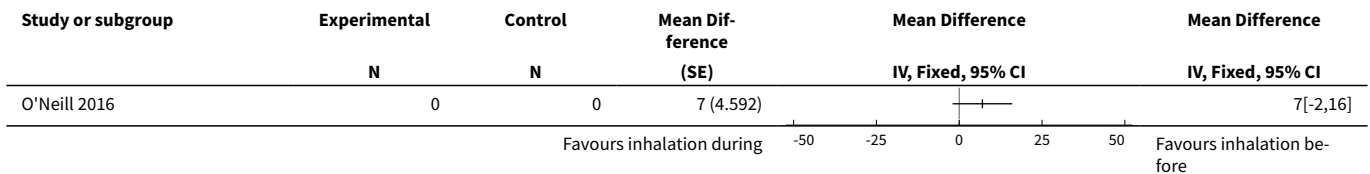
Analysis 1.8. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 8 Perceived efficacy (mm).



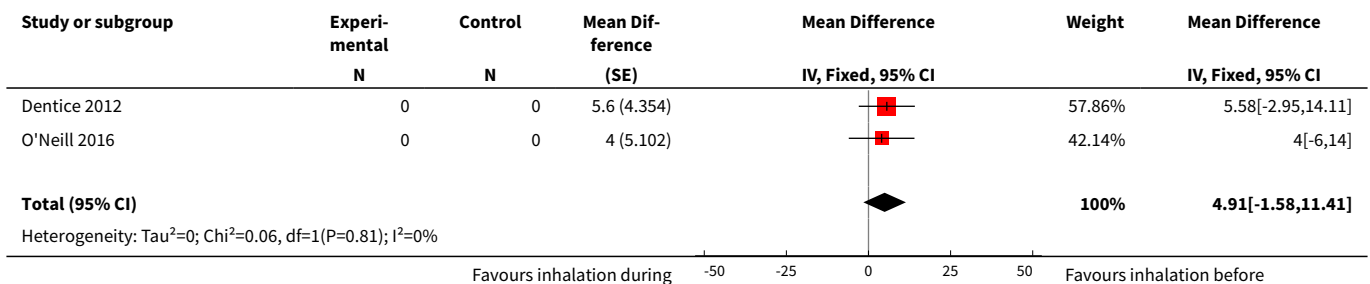
Analysis 1.9. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 9 Ease (mm).

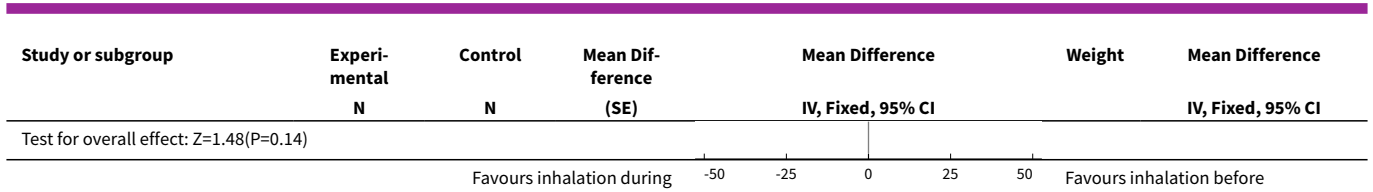


Analysis 1.10. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 10 Ease rated by therapist (mm).

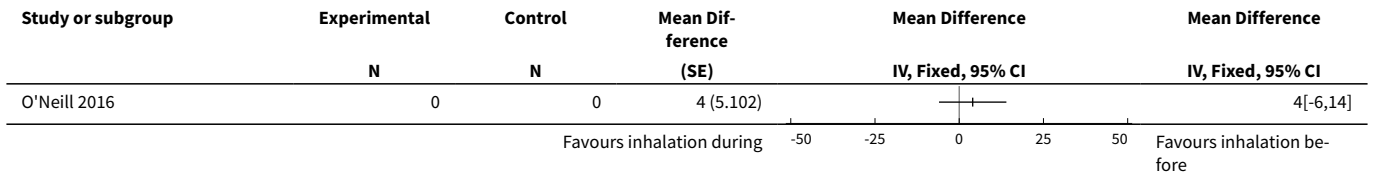


Analysis 1.11. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 11 Satisfaction (mm).

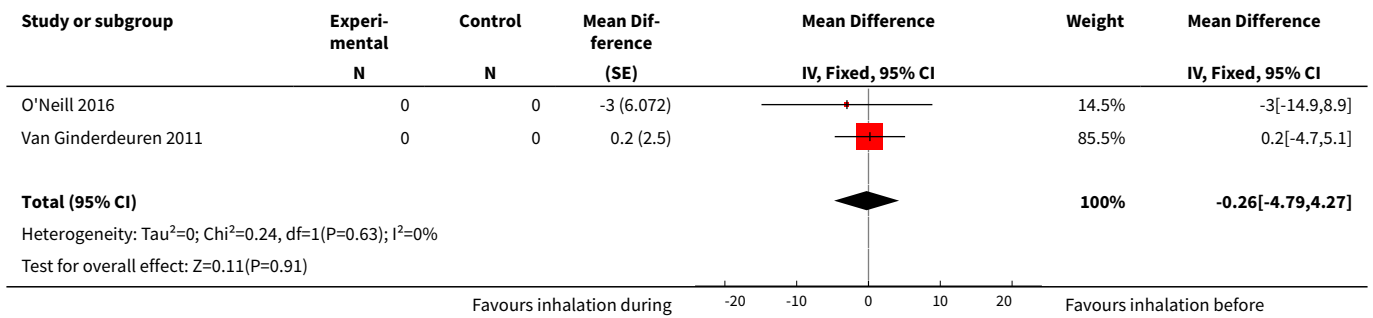




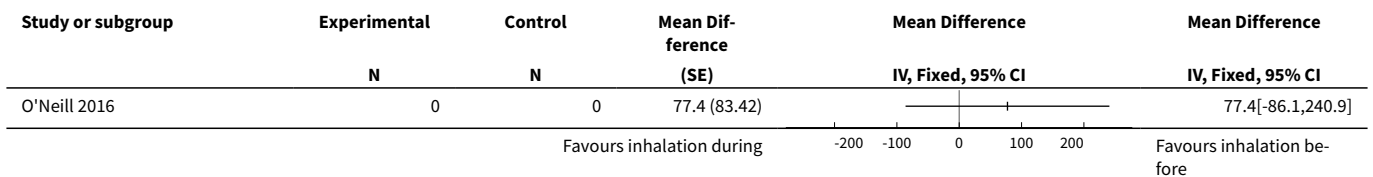
Analysis 1.12. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 12 Satisfaction rated by therapist (mm).



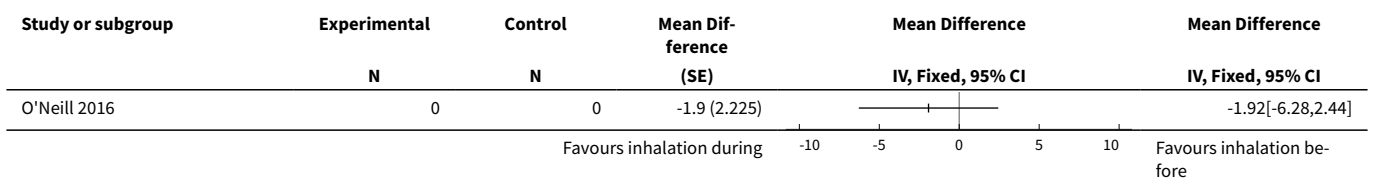
Analysis 1.13. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 13 Sputum wet weight immediately (g).



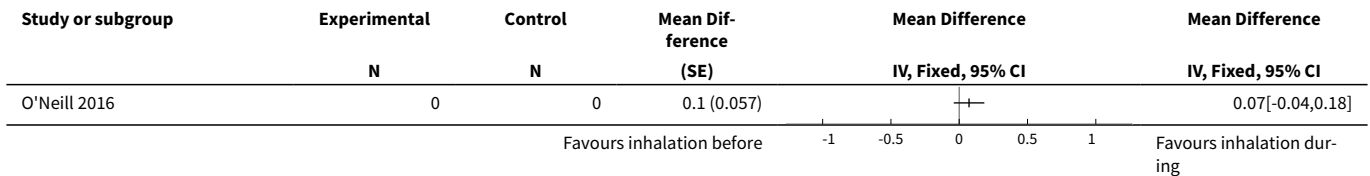
Analysis 1.14. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 14 Sputum wet weight next 24 hours (g).



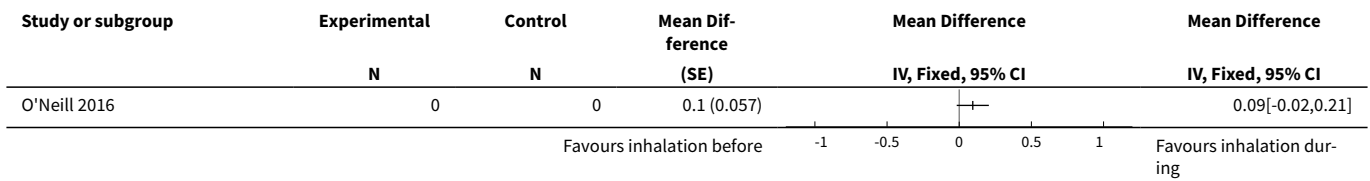
Analysis 1.15. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 15 FEF₂₅₋₇₅ (% pred).



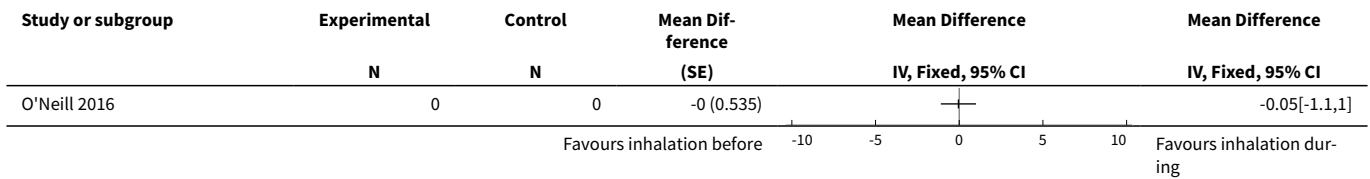
Analysis 1.16. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 16 FRC immediately (L).



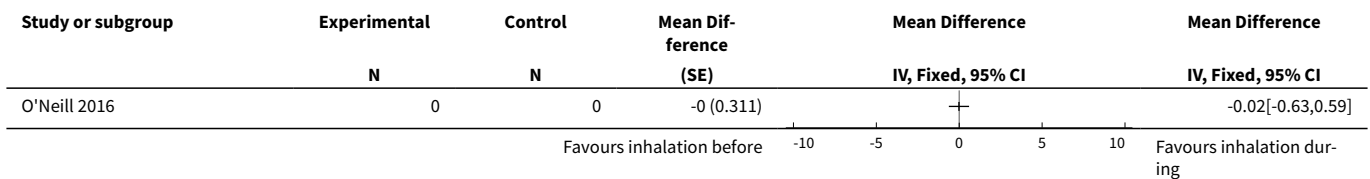
Analysis 1.17. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 17 FRC at 90 min (L).



Analysis 1.18. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 18 LCI immediately.



Analysis 1.19. Comparison 1 Inhalation before versus during airway clearance techniques, Outcome 19 LCI at 90 min.

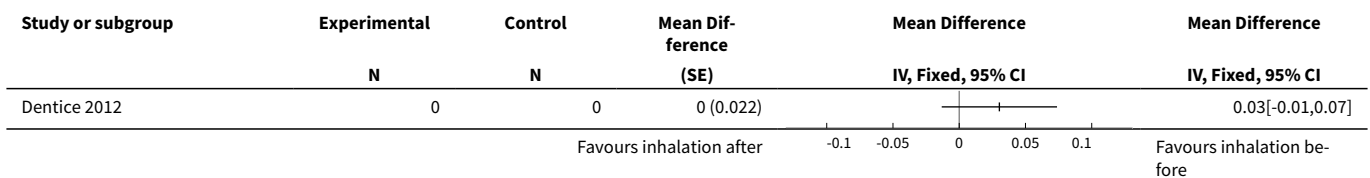


Comparison 2. Inhalation before versus after airway clearance techniques

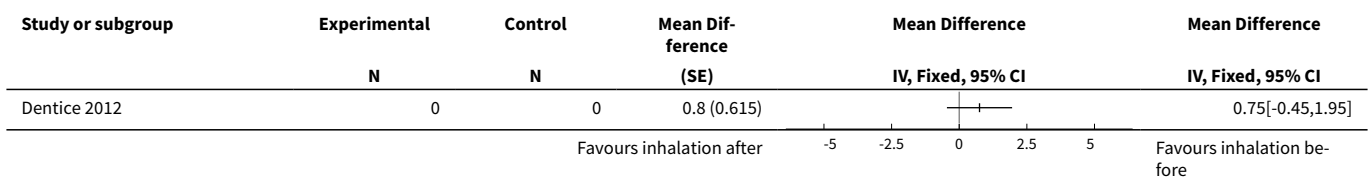
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV ₁ (L)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
2 FEV ₁ (% pred)	1		Mean Difference (Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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

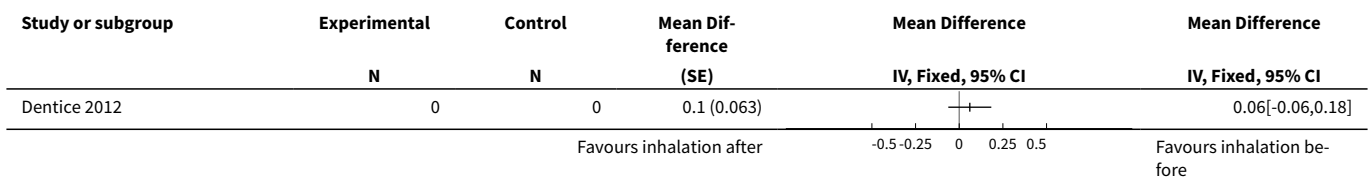
Analysis 2.1. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 1 FEV₁ (L).



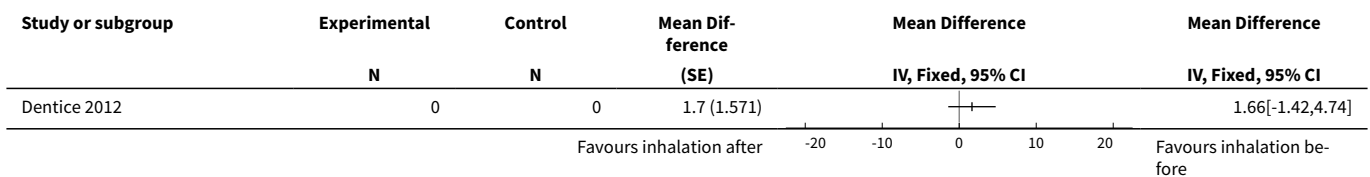
Analysis 2.2. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 2 FEV₁ (% pred).



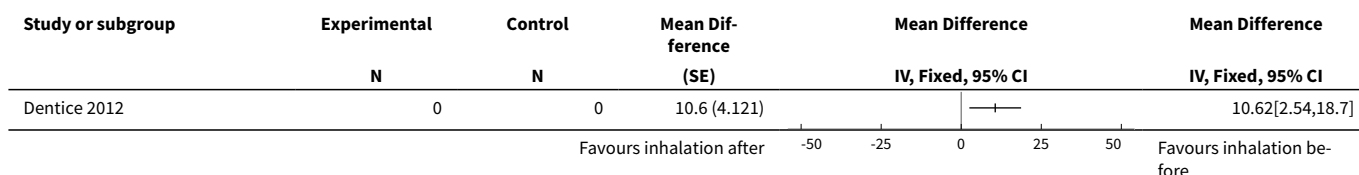
Analysis 2.3. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 3 FVC (L).



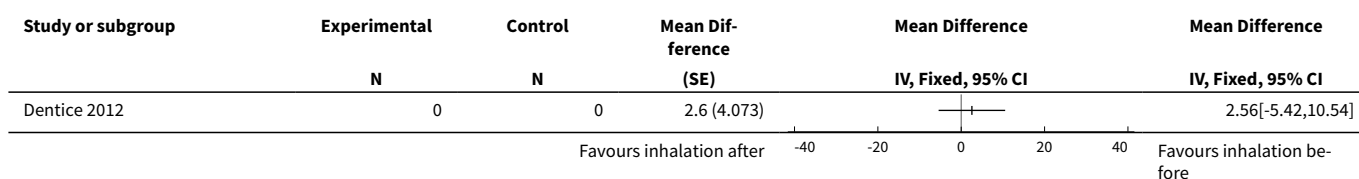
Analysis 2.4. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 4 FVC (% pred).



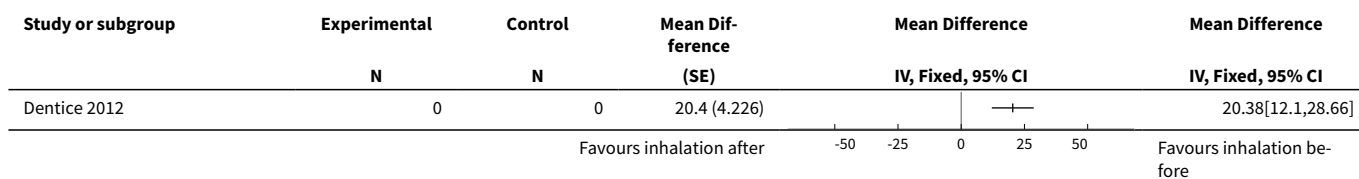
Analysis 2.5. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 5 Perceived efficacy (mm).



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



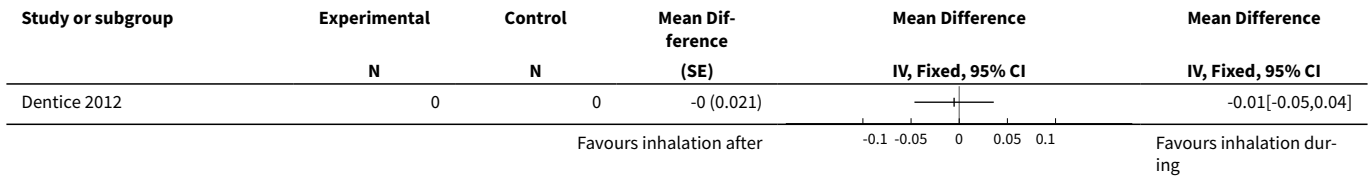
Analysis 2.7. Comparison 2 Inhalation before versus after airway clearance techniques, Outcome 7 Satisfaction (mm).



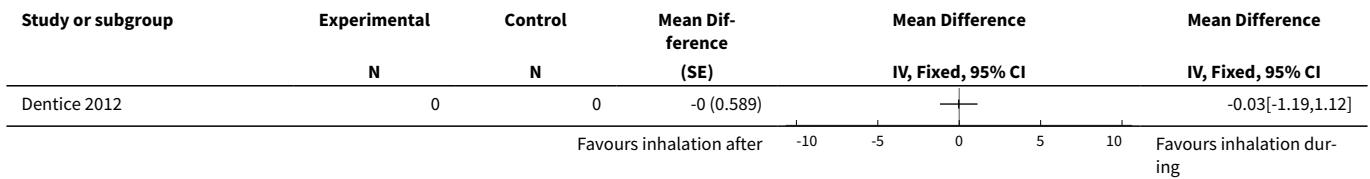
Comparison 3. Inhalation during versus after airway clearance techniques

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

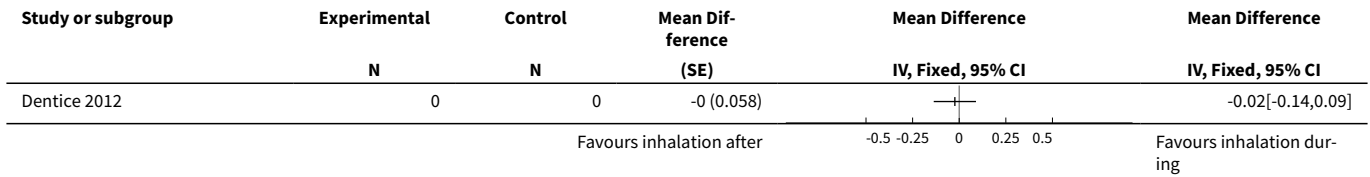
Analysis 3.1. Comparison 3 Inhalation during versus after airway clearance techniques, Outcome 1 FEV₁ (L).



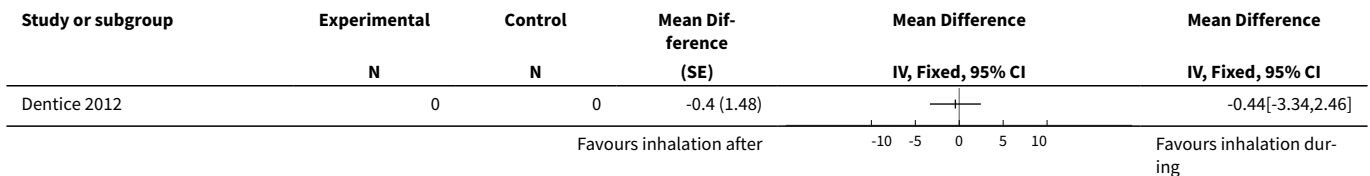
Analysis 3.2. Comparison 3 Inhalation during versus after airway clearance techniques, Outcome 2 FEV₁ (% pred).



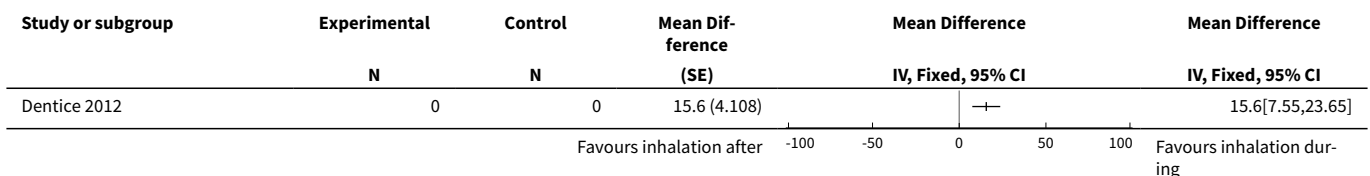
Analysis 3.3. Comparison 3 Inhalation during versus after airway clearance techniques, Outcome 3 FVC (L).



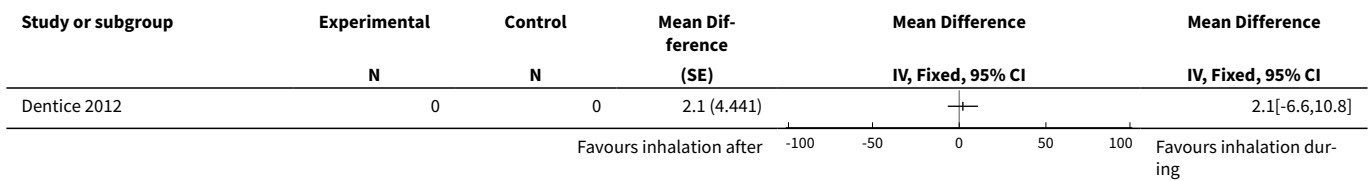
Analysis 3.4. Comparison 3 Inhalation during versus after airway clearance techniques, Outcome 4 FVC (% pred).



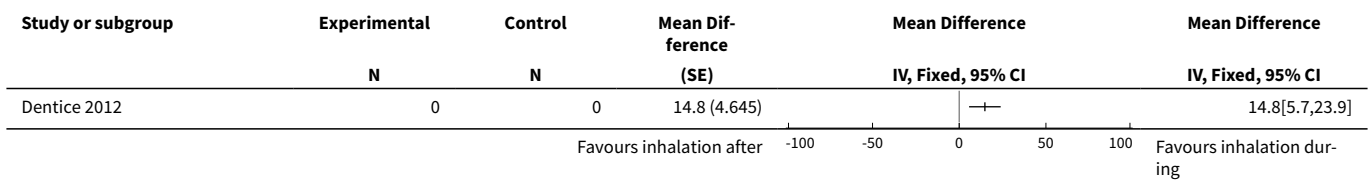
Analysis 3.5. Comparison 3 Inhalation during versus after airway clearance techniques, Outcome 5 Perceived efficacy (mm).



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



Analysis 3.7. 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

Appendix 3. ClinicalTrials.gov

1. Cystic fibrosis AND Hypertonic saline

WHAT'S NEW

Date	Event	Description
24 February 2020	New citation required but conclusions have not changed	The conclusions have not been not changed, however, one recommendation for future research has been added.
24 February 2020	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Cystic Fibrosis Trials Register identified seven potentially-eligible references to five trials, one was an additional reference to a study already awaiting classification (O'Neill 2016), which has now been included in the review.

HISTORY

Protocol first published: Issue 11, 2010
Review first published: Issue 2, 2012

Date	Event	Description
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).
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).

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.

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INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans