Nebulised hypertonic saline for cystic fibrosis (Review)

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ABSTRACT

Background
The lung disease in cystic fibrosis is characterised by impaired mucociliary clearance. Hypertonic saline (HS) has been shown to enhance mucociliary clearance in-vitro and this may act to lessen the destructive inflammatory process in the airways.

Objectives
To investigate the effects of treatment with nebulised hypertonic saline on people with CF compared to placebo and or other treatments that enhance mucociliary clearance.

Search strategy
We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group trials register which comprises references identified from comprehensive electronic database searches, handsearching relevant journals and handsearching abstract books of conference proceedings.

Date of the most recent search of the Group's register: October 2001.

Selection criteria
All controlled trials (any language) assessing the effect of hypertonic saline compared to placebo or other mucolytic therapy, for any duration or dose regimen in people with cystic fibrosis of any age or severity.

Data collection and analysis
All identified trials were independently reviewed by both reviewers & all data collected. Trial quality was assessed along with allocation concealment.

Main results
Fourteen controlled trials were identified. Nine trials met the inclusion criteria; these involved 235 participants with an age range of 6 to 46 years.

Two short-term trials of immediate effect on mucociliary clearance demonstrated that HS increased isotope clearance compared to control. Lung function as measured by improvement in Forced Expiratory Volume at one second (FEV1 l/min) was observed in four trials. When 3% to 7% saline was used in a volume of 10mls twice a day, in comparison to placebo, HS led to a significant increase in FEV1, WMD 12.20 (95%CI 4.30 to 20.10). In comparison to deoxyribonuclease (DNase) two trials used a similar concentration and volume of HS. Over a three week period the groups showed a similar increase in FEV1, WMD -1.60 (95%CI -11.16 to 7.96). However after 12 weeks treatment in participants with moderate to severe lung disease compared to DNase, HS 5mls twice a day showed less benefit to FEV1, WMD -13.00 (95%CI -22.46 to -3.54). No serious adverse events were noted.

Authors' conclusions
Nebulised hypertonic saline improves mucociliary clearance in short term clinical trials and appears to increase lung function compared to control. In comparison to DNase it may be less effective at improving lung function, after three months. At this stage there is insufficient evidence to support the use of hypertonic saline as routine treatment for people with cystic fibrosis.
SYNOPSIS

Nebulised saline can help clear mucus in the lungs of people with cystic fibrosis, but may not work as effectively as other options long term.

People with cystic fibrosis produce mucus in their lungs and airways (passages to the lungs) which is hard to clear, leading to infections and airways damage. Chest physiotherapy and/or drugs such as deoxyribonuclease are used to try and clear this mucus. Nebulised hypertonic saline is water (with a concentration of 3% or more salt) inhaled as a fine mist through a mask or mouthpiece. The review of trials found that 10ml of saline at 3% to 7% concentration, twice a day, helped clear mucus without significant adverse effects. However, it appears to be less effective than deoxyribonuclease at improving lung function in the medium term.

BACKGROUND

Cystic fibrosis (CF) is the most common fatal autosomal recessive genetic disorder in Caucasians. In 1989 the gene responsible was identified on the long arm of chromosome 7. This gene encodes for a protein named the cystic fibrosis transmembrane conductance regulator (CFTR) which functions as a chloride channel on the surface of epithelial cells. The altered CFTR is thought to result in defects of electrolyte transport which then cause increased water reabsorption across respiratory epithelia. This may lead to dehydration of the airway surface liquid which may prevent normal clearance of mucus (Davis 1996), although the precise mechanism by which CFTR causes abnormal mucus is still unknown. Treatments to improve sputum clearance, such as chest physiotherapy, are a major therapeutic aim in CF. Treatment with nebulised deoxyribonuclease (DNase) has been widely accepted to be of benefit in CF (Kearney 2000) and is thought to exert its major effect by enhancing sputum clearance.

In-vitro deposition of hypertonic saline onto the airway surface improves mucus clearance. Dasgupta (Dasgupta 1995) demonstrated that the addition of 3% hypertonic saline improved measures of sputum clearance. Hypertonic saline had a greater effect on mucus clearability in vitro than DNase (Dasgupta 1995). The postulated molecular mechanism of this effect is as follows: (i) Hypertonic saline breaks the ionic bonds within the mucus gel, which could reduce the degree of cross linking and entanglements and lower viscosity and elasticity (Ziment 1978). (ii) With chronic infection the mucin macromolecules develop fixed negative charges, causing increased repulsion. The addition of hypertonic saline increases the ionic concentration of the mucus and cause a conformational change by shielding the negative charges and thereby reducing repulsion. This would result in a more compact mucus macromolecule that would allow more effective clearance (Robinson 1997). (iii) In addition hypertonic saline induces an osmotic flow of water into the mucus layer, rehydrating secretions and thereby improving mucus rheology (Robinson 1997). In the long term this improvement in mucociliary function may reduce bacterial load and chronic inflammation within the airways and therefore reduce the decline in lung function that is consequent to this. Hypertonic saline is easy and inexpensive to produce. Therefore, it is important to determine if nebulised hypertonic saline improves outcomes in CF and to determine the frequency of adverse effects.

OBJECTIVES

To investigate the effects of treatment with nebulised hypertonic saline on people with CF compared to placebo and or other treatments that enhance mucociliary clearance.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies
Controlled clinical trials. Both random allocation and pseudo random allocation (where there is alternate allocation to treatment and control groups) were included.

Types of participants
People of all ages and of both sexes with CF diagnosed clinically or by sweat and genetic testing, including all degrees of disease severity.

Types of intervention
Nebulised hypertonic saline was compared either to placebo or, usual treatment or other mucus mobilising treatments. Hypertonic saline was defined as a concentration of saline greater than or equal to 3%. Limited to nebulisation delivered via a nebuliser using a mask or mouthpiece. Treatment was given as a minimum of a single dose.

Types of outcome measures
PRIMAR Y OUTCOMES

(1) Lung function (absolute change and change in % predicted): (a) forced expiratory volume at one second (FEV1); (b) forced vital capacity (FVC);

(c) lung volume (residual volume (RV) and total lung capacity (TLC)):
SECONdARY OUTCOMES

(3) Measures of sputum clearance, including measures of mucociliary clearance
(4) Measures of exercise capacity
(5) Measures of Quality of Life (QOL) and symptom scores
(6) 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;
(b) outpatient treatments (hospital in the home, unscheduled visits to the doctor).
(7) Medication delivery time
(8) Cost of treatment
(9) Adherence to treatment with hypertonic saline along with other treatments after hypertonic saline is added
(10) Adverse effects such as bronchospasm, cough and acute decline in pulmonary function. This acute decline will be limited to the immediate phase of receiving treatment with hypertonic saline to within the first three hours. This is described separately to longer term lung function data as it represents acute bronchospasm provoked by hypertonic saline.

S E A R C H S T R A T E G Y F O R I D E N T I F I C A T I O N O F S T U D I E S

See: Cystic Fibrosis and Genetic Disorders Group search strategy

Relevant trials were identified in the Cochrane CF and Genetic Disorders Group CF register of controlled trials. This register was compiled by conducting computerised searches of MEDLINE from 1966 to present and from EMBASE from 1974 to 1995. The register of controlled trials is updated every three months. Unpublished work has been identified by searching through the abstract books of the three major CF conferences; The International CF conference, the European CF conference and the North American CF conference.

The following terms were used in the search:
Mucolytic
Nebulised
Saline
Hypertonic

Review articles and bibliographies identified from this process were surveyed for additional citations & controlled trials.

Date of the most recent search of the Group's specialised register: October 2001.

M E T H O D S O F T H E R E V I E W

Two reviewers independently selected the trials to be included in the review. If disagreement arose on the suitability of a trial for inclusion in the review or on its quality, we reached a consensus by discussion. Each reviewer assessed the methodological quality of each trial. In particular, reviewers examined details of the generation of allocation sequence, the concealment of treatment allocation schedule, whether the trial was blinded, whether intention to treat analyses were possible from available data and if the number lost to follow up or subsequently excluded from the study was recorded. The reviewers using standard data acquisition forms independently extracted data.

For binary outcome measures, data on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow-up were sought to allow an intention to treat analysis. We calculated a pooled estimate of the treatment effect for each outcome across the studies, (the odds of an outcome among treatment allocated participants to corresponding odds among controls). For continuous outcomes, we recorded either a mean change from baseline for each group or mean post-treatment/ intervention values and standard deviation for each group. We calculated a pooled estimate of treatment effect by calculating the weighted mean difference where appropriate. Where trials were of a cross-over design the means and standard deviations were entered into RevMan for the whole time period of the trial. We acknowledge this may cause some inaccuracy in the analysis and plan to re-enter all cross-over data when RevMan 4.2 is available. At this stage as the results entered into RevMan appear to reflect those found in the original articles there does not appear to have been a distortion of the results.

Heterogeneity between trial results was tested using standard chi-squared test. For future updates of the review, when appropriate, where between trial variability is not statistically significant we will carry out a fixed effect analysis and if the between trial heterogeneity is statistically significant we will perform a random effects analysis. We plan to perform a sensitivity analysis based on methodological quality of the studies, including and excluding quasi-randomised studies.

The comparisons were:
(1) inhaled hypertonic saline versus placebo - isotonic saline (or a placebo other than isotonic saline);
(2) inhaled hypertonic saline versus inhaled recombinant human DNase;
(3) inhaled hypertonic saline versus other inhaled treatments that increase mucociliary clearance.
The following strength of hypertonic saline were considered:
(1) hypertonic saline 5 to 7%;
(2) hypertonic saline greater than 7%.

The following volumes will also be considered:
(1) less than 5mls;
(2) 5 to 10mls;
(3) greater than 10mls.

DESCRIPTION OF STUDIES

Summary details are given in the 'Characteristics of Included studies' section.

Fourteen controlled trials were identified, nine trials met the inclusion criteria with a total of 235 participants, the age range for them was six to 46 years (Weller 1980; Eng 1996; Riedler 1996; Robinson 1996; Chadwick 1997; Robinson 1997; Ballmann 1998; Robinson 1999; Suri 2001). Of these, seven were published as papers and two were published in abstract form (Chadwick 1997; Ballmann 1998).

The diagnostic criteria for CF in the participants was stated by Eng and this was on the basis of known positive sweat chloride tests (Eng 1996) and by Suri (Suri 2001) on the basis of a positive sweat test or the presence of two common genetic mutations. In all the other trials it was only stated that the participants had CF. In the Ballmann trial, inclusion and exclusion criteria were not stated (Ballmann 1998). In Eng participants had to be able to perform spirometry, have cough and daily sputum production, agree to do regular chest physiotherapy at home, have an FEV1 greater than 20% predicted at baseline and be on stable medications for the previous 14 days (Eng 1996). In Suri inclusion criteria were: age 5 to 18 years, ability to perform spirometry, to be currently on rhDNase or have an FEV1 less than 70% predicted and to be clinically stable with no exacerbations or change in medications in the last 14 days. In the Suri trial participants were excluded if they were colonised with Burkholderia Cepacia (Suri 2001). In two trials by Robinson the participants had to be in a stable clinical condition without any change to their medications (Robinson 1996; Robinson 1997). The Riedler trial was unique in that they selected 10 consecutive adolescents admitted with an exacerbation of their lung disease, all had productive cough (Riedler 1996). Robinson (1999), clearly stated that they excluded people if CF who were clinically unstable, defined as an exacerbation in the previous four weeks. Weller (Weller 1980) stated that all participants received routine treatment for five years. The other trials used mean FEV1 as a percent predicted or FVC as a percent predicted to assess severity. Suri included people with CF with at least moderate lung disease, to compare hypertonic saline to to rhDNase in a population that would be prescribed DNase in clinical practice (Suri 2001). Consequently their participants have more severe lung disease at baseline, mean FEV1 % predicted 48% (range 14 to 77%). Only the 1997 Robinson trial included a participant with an FEV1% predicted of less than 30% (Robinson 1997).

Baseline sputum microbiology was stated in four trials. Robinson had 10 out of 10 participants with Pseudomonas aeruginosa in their sputum, 5 out of 10 with Staphylococcus aureus and none with Burkholderia cepacia (Riedler 1997). Riedler had 10 out of 10 with P. aeruginosa in their sputum, no B. cepacia and the presence of other organisms was not stated (Riedler 1996). In Robinson, 10 of 12 participants were colonised with P. aeruginosa, seven had Staphylococcus aureus (including two who also had P. aeruginosa) and four had Aspergillus fumigatus (Robinson 1999). In the Suri trial 48% had P. aeruginosa, 39% Staphylococcus aureus and 2% Stenotrophomonas maltophilia (Suri 2001). Weller mentioned bacterial growth but no detail was given (Weller 1980).

In the trials by Eng, Suri and Robinson (Eng 1996; Suri 2001; Robinson 1996; Robinson 1997; Robinson 1999) an ultrasonic nebuliser was used to deliver hypertonic saline. While Ballmann and Riedler used a high output jet nebuliser (Ballmann 1998; Riedler 1996). Different concentrations of hypertonic saline were used and this is outlined in detail in the ‘Characteristics of Included Studies’. Four out of seven of these trials used isotonic (0.9%) saline as a control (Eng 1996; Riedler 1996; Robinson 1996; Robinson 1997) Robinson 1996 compared nebulised hypertonic saline, amiloride and amiloride plus hypertonic saline with isotonic saline and with voluntary cough. While Robinson (Robinson 1997) compared differing concentrations of nebulised hypertonic saline (3%, 7%, and 12%) with isotonic saline and voluntary cough. Ballmann compared the efficacy of three weeks of nebulised 5.75% saline (10mL) to 2.5mg recombinant DNase (Ballmann 1998). Robinson (Robinson 1999) compared hypertonic saline 6% to 0.9% saline with matched voluntary cough, Mannitol 300mg, and placebo capsules with matched voluntary cough. Weller (Weller 1980) compared hypertonic saline 7% (5mL) to Mistabron 20% (a mucolytic agent). Suri 2001 compared hypertonic saline 7% (5mL) BD (twice daily) to rhDNase 2.5mg daily and 2.5mg alternate daily.

Additional treatments were also used in association with the hypertonic saline. All the trials with the exception of Weller and Chadwick pre-treated participants with short acting beta-agonists (Weller 1980; Chadwick 1997). In the Suri trial only pre-treated participants who were already using bronchodilators or if their FEV1 fell > 15% after the test dose (Suri 2001). Riedler used the hypertonic saline as an adjunct to physiotherapy and an exercise programme and all participants had intravenous antibiotics (Riedler 1996). Eng had as an inclusion criteria, that participants perform physiotherapy at home and delivered hypertonic saline prior to the participants’ regular physiotherapy session (Eng 1996). The place of chest physiotherapy is likely to be an important contributor to mucolytic therapy but its role as a confounder was not addressed in any of the trials.
METHODOLOGICAL QUALITY

In no trials were the interventions blinded as all investigators stated this was not possible due to the discernible taste of hypertonic saline.

The Weller trial was a randomised control trial (Weller 1980). Adverse events were described. It was reported to be single blinded but the issue of taste of HS was not addressed and blinding was not described. There was a clear description of dropouts and withdrawals. Methods of statistical analysis were described.

The Eng trial reported a randomised parallel trial (Eng 1996). A clear description of adverse effects was given and withdrawals accounted for.

The Riedler trial reported that participants were randomised using a coin toss. The methods of statistical analysis were described. The methods used to measure adverse effects were not mentioned and there was no description of withdrawals and no exclusion criteria were cited (Riedler 1996).

The 1996 Robinson trial performed a prospective cross-over trial in which allocation was not randomised. The methods of analysis were described and adverse effects but no exclusion criteria were stated (Robinson 1996).

The Chadwick trial was a single blind randomised trial (Chadwick 1997). This was reported as an abstract and no details were given concerning inclusion criteria, withdrawals, randomisation method or statistical analysis and the issue of taste of HS were not addressed.

The 1997 Robinson trial was a randomised prospective design (Robinson 1997). Inclusion criteria were CF, stability of their disease (not defined) except there could be no change in their medications. The randomisation process was not defined; there was no mention of withdrawals and no measure of adverse effects given.

The Ballmann trial was reported in abstract form only (Ballmann 1998). The trial was described as randomised, but the method of randomisation was not stated and there was no description of withdrawals, inclusion and exclusion criteria or the methods of statistical analysis.

The 1999 Robinson trial was a randomised control cross-over design (Robinson 1999). Inclusion criteria were a diagnosis of CF and clinically stable disease defined by an absence of an exacerbation in the previous four weeks. There was no mention of withdrawals. The methods of analysis were described and a clear description of adverse events given.

The Suri trial followed a randomised cross-over design, there was a clear description of adverse events (Suri 2001). This trial compared DNase daily and alternate daily to hypertonic saline 7% but did not have a placebo arm.

RESULTS

PRIMARY OUTCOMES

(1) Lung function
(a) hypertonic saline versus placebo (isotonic saline)
Eng (Eng 1996) examined mean percentage change in FEV1 from baseline at two weeks and demonstrated a significant improvement in the group treated with hypertonic saline, WMD 12.20 (95%CI 4.30 to 20.10). A similar improvement in FVC in the hypertonic saline group failed to reach statistical significance.

(b) Hypertonic saline versus DNase
Suri measured the mean increase in FEV1 from baseline comparing hypertonic saline 3% 5mls (3% increase) to daily (16% increase) and alternate daily (14% increase) DNase (Suri 2001). Comparisons between daily hypertonic saline and daily DNase have been made. Suri found that DNase led to a greater increase in FEV1 compared to hypertonic saline, WMD -13.00 (95%CI -22.46 to -3.54) (Suri 2001). Ballmann did not demonstrate a significant difference between hypertonic saline and DNase, WMD -1.60 (95%CI -11.16 to 7.96) (Ballmann 1998). The results were not pooled because the duration of the interventions in the two trials was very different: three weeks for the Ballmann trial and three months for the Suri trial (Ballmann 1998; Suri 2001). Both Ballmann and Suri compared the number of participants who improved their FEV1 by 10% or more from baseline after treatment and found no significant difference between hypertonic saline and DNase, relative risk (RR) 0.75 (95%CI 0.49 to 1.15) (Ballmann 1998; Suri 2001).

(c) hypertonic saline versus other treatments that enhance mucociliary clearance
Weller compared Mistabron 20% 3mls BD to hypertonic saline 7% 3mls BD (Weller 1980). They divided their participants into sputum producers (SP) and non-sputum producers (NSP). The SP given Mistabron increased peak expiratory flow (PEF) (+7 change from baseline L/min) compared to hypertonic saline (-2, p<0.02). There was no significant difference in PEF in the NSP group. FVC was not significantly different in either group. V max 50% vital capacity (VC) increase in the SP with Mistabron (+10) compared to hypertonic saline (0, p<0.005). In the NSP hypertonic saline improved V max 50% VC (+14) compared to Mistabron (-5) but this was not significant. In the SP group RV/TLC improved with hypertonic saline (+1) compared to Mistabron (-10) but not on RV/TLC whilst hypertonic saline had (-6) change, again this did not reach significance. Only 3mls of 7% hypertonic saline was used in the Weller trial (Weller 1980).

(2) Mortality
No trials reported on mortality as an outcome.

SECONDARY OUTCOMES

(3) Sputum Measures
(a) Hypertonic saline versus isotonic saline

The Robinson trials looked at radiolabelled aerosol clearance to assess mucociliary clearance (Robinson 1996; Robinson 1997; Robinson 1999). In this method the participant was given the radiolabelled aerosol from an ultrasonic nebuliser and serial lung scans performed. Two of the Robinson trials (Robinson 1996; Robinson 1997) showed that hypertonic saline increased radioisotope clearance compared to isotonic saline controls (Robinson 1996, p<0.05) (Robinson 1997, p<0.01). The 1997 Robinson trial showed that increasing concentrations of hypertonic saline also had an effect, with a significant difference between hypertonic saline 3% and hypertonic saline 12%, favouring the higher concentration but no significant difference between hypertonic saline 7% and hypertonic saline 12% (Robinson 1997). A comparison was made between the two trials for isotope clearance at 90 to 120 minutes. This favoured treatment with a weighted mean difference of 10.73 (95%CI 4.17 to 17.28). In the Robinson trials (Robinson 1996; Robinson 1997) mucociliary clearance was then measured as Area Under the Curve (AUC), the lower the value of AUC the faster the clearance. Robinson (1997) showed that hypertonic saline 7% and hypertonic saline 12% were significantly different from isotonic saline. In the 1996 Robinson trial the results for AUC showed hypertonic saline, hypertonic saline and amiloride alone (Robinson 1996). Combined analysis of the two trials favoured treatment with a weighted mean difference of -212.06 (95%CI -271.64 to -152.48).

(b) Hypertonic saline versus other agents that increase mucociliary clearance

The Robinson 1996 trial looked at the added effect of amiloride to hypertonic saline and amiloride alone (Robinson 1996). There was no additional difference with amiloride and amiloride alone was not significantly different from isotonic saline. The Robinson trials (Robinson 1997; Robinson 1999) showed hypertonic saline 6% was superior to isotonic saline 0.9% with matched voluntary cough. Mannitol 300mg was superior to placebo with matched voluntary cough. There was no significant difference between mannitol and hypertonic saline.

Weller described no significant difference in sputum volume, colour or cough frequency between the groups. There was no change in sputum bacteriology or the number of courses of antibiotics prescribed (Weller 1980).

(4) Exercise capacity

(a) hypertonic saline versus isotonic saline

Eng demonstrated a significant improvement in exercise tolerance using a visual analogue scale (Eng 1996).

(b) hypertonic saline versus DNase

Suri measured exercise tolerance using a three minute step test at each visit along with oxygen saturation during exercise and a visual analogue score for dyspnoea (Suri 2001). They reported no significant differences between the groups.

(5) Symptom scores

(a) Hypertonic saline versus isotonic saline

Two trials assessed symptoms using visual analogue scales, both used 10cm scales ranging from -5 to +5. One trial (Eng 1996) found significant improvements in symptoms for quality of sleep and feeling of cleared chest measured after one and two weeks of treatment with hypertonic saline 6%. The Riedler trial looked at a similar visual analogue scale for feeling of cleared chest alone measured four days after treatment (Riedler 1996). They demonstrated a significant difference in their first block of 10 participants between hypertonic saline 6% and isotonic saline. The results of the two studies were pooled. This demonstrated a result favouring treatment with a weighted mean difference 0.97 (95%CI 0.35 to 1.60).

(b) Hypertonic saline versus DNase

Suri assessed symptoms using the quality of well being self-administered form 1.04 (Suri 2001). They reported there was no significant difference in scores between the groups although data are unavailable at this time.

(c) Hypertonic saline versus other treatments to increase mucociliary clearance

In the 1996 trial, Robinson used a visual analogue scale to assess need to cough. Both hypertonic saline 6% and mannitol 300mg were significantly different from isotonic saline controls (Robinson 1996).

(6) Pulmonary exacerbations

(a) Hypertonic saline versus DNase

Suri described pulmonary exacerbations during the trial with 15 episodes occurring during treatment with hypertonic saline, 18 with daily DNase and 17 with alternate DNAse, the RR of an exacerbation occurring while on hypertonic saline was not different compared to daily DNase 0.83 (95%CI 0.48 to 1.44) (Suri 2001).

(7) Delivery time

(a) Hypertonic saline versus DNase

Ballmann compared delivery time in minutes between hypertonic saline 5.85% 10mls BD and DNase 2.5mg BD and found that hypertonic saline took significantly longer to nebulise, WMD 31 minutes (95%CI 24.44 to 37.56) (Ballmann 1998).

(b) Hypertonic saline versus over treatments that increase mucociliary clearance

Robinson compared time taken to nebulise hypertonic saline 6% (4.4mls) to mannitol 300mg and found hypertonic saline took less time, WMD -6.1minutes (95%CI -7.32 to -4.86) (Robinson 1999).

(8) Cost

(a) Hypertonic saline versus DNase

Ballmann (Ballmann 1998) and Suri (Suri 2001) compared cost of treatment between DNase and hypertonic saline. Ballmann compared one month of hypertonic saline treatment with DNase (2427DM) to hypertonic saline (86DM) (Ballmann 1998). Suri...
In the Eng trial there were similar reports of increased cough and was directly related to treatment (Eng 1996). In the hypertonic haemoptysis, one participant in the hypertonic saline group had one complained of chest tightness and one of throat irritation, with none in the isotonic saline group complaining of these symptoms.

In the Eng trial there were similar reports of increased cough and haemoptysis, one participant in the hypertonic saline group had to withdraw because of haemoptysis though it was not clear if this was directly related to treatment (Eng 1996). In the hypertonic saline group one complained of chest tightness and one of throat irritation, with none of the participants fell significantly with hypertonic saline.

The Chadwick trial (Chadwick 1997) demonstrated that participants with an FEV1 40 to 70% at baseline had a significant fall in FEV1 following isotonic saline, while none of the participants described higher scores for throat irritation on a VAS compared to receiving hypertonic saline, WMD 5.20 (95% CI -0.59 to 10.99) (Robinson 1999). Participants who received hypertonic saline described coughing at the beginning of treatment as to they were encouraged to cough on the control days to match the active day’s cough so as not to confound the results of the mucociliary clearance data.

(c) Hypertonic saline versus other treatments that increase mucociliary clearance
In the 1999 Robinson trial, mannitol was regarded as more irritant than the control on VAS. FEV1 fell significantly five minutes after treatment with both mannitol and hypertonic saline 6% to a smaller degree compared to control (p=0.004) however by 95 minutes there was no significant difference between the groups (Robinson 1999). In the Weller trial the group given Mistabron and hypertonic saline described coughing at the beginning of their inhalations, no other serious adverse events occurred (Weller 1980).

DISCUSSION
The pulmonary complications of CF continue to have the greatest impact on mortality and morbidity. Recurrent infection and tenacious, difficult to clear mucus, characterise the disorder, particularly as lung function declines.

Treatment to improve mucociliary clearance with nebulised DNase is known to be effective in improving lung function in CF and has been adopted in most countries. However the long term efficacy of DNase is still a matter of debate (Kearney 2000). Nebulised DNase is an expensive treatment and in many countries its use is restricted to those who have moderate degrees of impairment of lung function, age greater than five years and who demonstrate an improvement in pulmonary function tests during a trial period (Ramsey 1994). This effectively means that a significant proportion of people with CF are ineligible for this form of treatment. There also remain individuals whose lung function does not improve with DNase or are unable to tolerate it due to side effects Kearney 2000 and an alternative agent to enhance mucociliary clearance would be desirable. In addition DNase is thought to increase mucociliary clearance by breaking down DNA debris in the sputum, however this is likely to be only one of many factors that reduce mucociliary clearance in CF and agents that target alternative abnormalities and increase mucociliary clearance may have additive effects in combination with DNase.

Hypertonic saline represents a potential alternative or supplementary therapy to improve mucociliary clearance to nebulised DNase. We reviewed the available literature to determine what evidence was available to support the use of nebulised hypertonic saline in CF. In general the amount of information available from trials of hypertonic saline in CF was limited due to their small size and medium term (less than three months hypertonic saline) duration.

An immediate effect on measures of mucociliary clearance was demonstrated over isotonic saline and cough alone in a series of trials from Robinson et al (Robinson 1996; Robinson 1997; Robinson 1999) and Riedler (Riedler 1996) that demonstrated increase sputum clearance. They showed that a dose of 7% hypertonic saline was more effective than 3%, but no significant
advantage was gained by increasing the dose to 12% or by adding amiloride. While they performed a dose response effect of varying concentrations of saline they did not look at the impact of the volume nebulised.

Four trials looked at the effect of hypertonic saline on lung function. Eng demonstrated a significant increase in FEV1 compared to isotonic saline control measured after two weeks (Eng 1996). Ballmann compared hypertonic saline 5.75% 10mls BD to nebulised DNase 2.5mg and found that in both groups FEV1 improved to a similar degree in three weeks (Ballmann 1998). In contrast, Weller who used only 5mls of hypertonic saline found that it did not significantly improve pulmonary function, though Mistabron did (Weller 1980). In addition in the larger and better-designed trial by Suri (Suri 2001), hypertonic saline 7% 5mls BD was compared to daily and alternate daily DNase 2.5mg. The participants who treated with either DNase regimen had a significant improvement in lung function from baseline, but when treated with hypertonic saline there was an increase of only 3% from baseline, less than seen in Eng and Ballmann (Eng 1996; Ballmann 1998). In both of these trials 10mL of hypertonic saline was used compared to 5mls used by Suri (Suri 2001) and Weller (Weller 1980), this raises the possibility that the effectiveness of treatment may also depend on the total volume of saline nebulised and this may account for the lower effect size seen by Suri. In addition Suri found a wide variation in response to treatment with both DNase and hypertonic saline, with over 50% demonstrating an increase in FEV1 of greater than 10% with DNase and 35% with hypertonic saline. Thus despite the overall reduced effect seen with hypertonic saline on lung function, in individuals, both DNase and hypertonic saline have the potential to substantially improve lung function in the medium term. The wide variation seen in response to both hypertonic saline and DNase raises the possibility that there may be subgroups of people with CF who are more likely to respond to efforts to improve mucociliary clearance. It also suggests that some individuals may respond better to one treatment compared to the other and physicians may wish to consider this particularly in individuals who fail to respond to DNase. None of the trials were of sufficient duration or size to assess mortality and while some evidence is available on the impact on lung function up to three months hypertonic saline this is of insufficient duration to infer any effect on overall survival.

Symptom improvement was assessed by Robinson and Eng using simple visual analogue scores to measure improvements in symptoms in response to hypertonic saline and found that there was an improvement in feelings of better chest clearance, exercise tolerance and quality of sleep (Eng 1996; Robinson 1996). Suri found no differences between those treated with DNase and hypertonic saline for 12 weeks in terms of change in exercise tolerance, dyspnæa, oxygen saturation during exercise and symptom score (Suri 2001). All treatment arms experienced a high frequency of pulmonary exacerbations, but this may be a reflection of the severity of the groups underlying lung disease.

Delivery time for hypertonic saline appears longer compared to DNase and this may have implications for adherence to treatment. Only Suri examined adherence, which appeared high and comparable to DNase in their three month trial (Suri 2001). However a trial of longer duration is likely to be needed to assess the long term impact of hypertonic saline as an additional treatment. In terms of cost both Ballmann and Suri found hypertonic saline to be less expensive compared to DNase (Ballmann 1998; Suri 2001).

The only trials in which adverse events were reported in detail were those by Eng, Robinson and Suri (Eng 1996; Robinson 1999; Suri 2001). Acute bronchospasm remains a concern with hypertonic saline. Despite pre-treatment of participants with bronchodilators, three were excluded from Suri due to a fall in FEV1 greater than 15% (Suri 2001) and in Robinson there was a tendency towards a fall in FEV1 compared to control. Symptoms such as cough and throat irritation do appear to be more frequent in hypertonic saline compared to control but this does not appear to have been a serious enough side effect to have led to participants withdrawals. In the Eng trial one participant did withdraw from the hypertonic saline group because of haemoptysis it is not proven that this was a consequence of the treatment (Eng 1996).

Authors' conclusions

Implications for practice

Hypertonic saline has been shown in a concentration of 5 to 7% when delivered by an ultrasonic nebuliser to improve mucociliary clearance. In the medium term it does not appear to be associated with serious side effects, though bronchospasm can still occur despite pre-treatment with bronchodilators. While there is evidence that it improves lung function compared to control, this improvement appears to be less than seen with DNase. There is insufficient evidence to recommend the use of hypertonic saline for routine treatment in CF, data with effects on lung function, quality of life, frequency of exacerbations of chest disease and with longer-term follow-up are needed before this can be recommended. The variation in response seen in individuals to both DNase and HS raises the possibility that certain individuals will respond better to one agent compared to the other. At this stage it would be reasonable to conduct N=1 trials on patients who fail to respond, are ineligible or are unable to tolerate DNase, with HS as an alternative agent to increase mucociliary clearance. Unfortunately there are no data on effects of HS in combination with DNase.

Implications for research

There is a need to carry out more research into the effects and potential adverse effects of hypertonic saline in CF over a longer period, particularly in subjects who are unable to use DNase and in combination with DNase. Concern remains as to whether hypertonic saline has the potential to cause bronchospasm and the
theoretical concern that it may impair mucosal defence mechanisms and increase the risk of endobronchial infection.

A dose response for volume of hypertonic saline needs to be determined, along with assessing the time this will take to nebulise, the cost and the impact on compliance.

This could be addressed by a prospective randomised controlled trial with a factorial design with four groups: placebo, DNase, HS and both for a period of at least six months but preferably 2 years. This would be able to monitor the short-term and long-term changes in pulmonary function tests and formal measures of exercise tolerance, (for example the six minute walk or exercise testing), frequency of exacerbations of lung disease, the use of antibiotics for lung disease and detect changes in formal quality of life scores.

NOTES
With this update significant changes to style were made particularly in the order of the outcomes and the presentation of the results.

The Suri 2001 trial was added and this contained a large amount of additional information particularly concerning the effect of hypertonic saline versus DNase on lung function.

ACKNOWLEDGEMENTS
The authors would like to thank Dr G Ryan, Sir Charles Gardiner Hospital Perth Western Australia for editorial advice.

In addition to Dr P Gibson and Ms J Coughlin of the Airways research Centre John Hunter Hospital Australia for technical assistance.

We would also like to thank the authors of Robinson 1996 and Suri 2001 for providing additional information regarding their trials.

POTENTIAL CONFLICT OF INTEREST
None known

SOURCES OF SUPPORT
External sources of support
- No sources of support supplied

Internal sources of support
- No sources of support supplied

REFERENCES


Eng BM, Riedler J, Eng P, Robertson CF. Inhaled hypertonic saline as an adjunct to chest physiotherapy in cystic fibrosis; the three year clinical experience [abstract]. Pediatric Pulmonology 1996;Suppl 13:306.


Weller 1980 (published data only)

References to studies excluded from this review
Genkova 1998

Hofmann 1997

King 1997

Additional references
Dasgupta 1995

Davis 1996

Kearney 2000

Ramsey 1994

Robinson 1997

Ziment 1978

References to other published versions of this review
Wark 1999

Wark 2000

* Indicates the major publication for the study

T A B L E S

Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Ballmann 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised cross-over trial</td>
</tr>
<tr>
<td>Participants</td>
<td>n = 14</td>
</tr>
<tr>
<td></td>
<td>males=8</td>
</tr>
<tr>
<td></td>
<td>females=6</td>
</tr>
<tr>
<td></td>
<td>FEV1 % predicted had to be greater than 40%</td>
</tr>
<tr>
<td>Interventions</td>
<td>Pre-treated salbutamol 200 mcg MDI inhaled</td>
</tr>
<tr>
<td></td>
<td>Hypertonic saline 5.85% 10mls BD for three weeks</td>
</tr>
<tr>
<td></td>
<td>Pulmazyme 2.5mg BD for three weeks</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Change in FEV1 as a % of predicted</td>
</tr>
<tr>
<td></td>
<td>Nebulisation time</td>
</tr>
<tr>
<td></td>
<td>Comparison of cost, measured in Deutches Marks</td>
</tr>
<tr>
<td>Notes</td>
<td>Abstract only</td>
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</table>
**Characteristics of included studies (Continued)**

<table>
<thead>
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<th>Methods</th>
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<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chadwick 1997</td>
<td>Randomised cross-over trial</td>
<td>n = 15</td>
<td>Isotonic saline, hypertonic saline 3.5% and hypotonic saline</td>
<td>Change in FEV1 as a % of predicted Nebulisation</td>
<td>Abstract only</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eng 1996</td>
<td>Randomised parallel group trial, unblinded</td>
<td>n = 58</td>
<td>Pre-treated salbutamol 600mcg MDI and volumatic spacer device. Hypertonic saline 6% 10mls BD for 2 weeks (treatment group) Isotonic saline BD for two weeks (control group)</td>
<td>Mean change in FEV1 at two weeks Mean change FVC at two weeks VAS for cleared chest at one and two weeks VAS for dyspnoea VAS for fatigue VAS for appetite VAS for exercise tolerance VAS for quality of sleep VAS for general well being Adverse effects; increased cough, haemoptysis, chest tightness and pharyngitis</td>
<td>Abstract only</td>
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</table>

**Allocation concealment**

- D
- C
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Riedler 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised cross-over trial</td>
</tr>
</tbody>
</table>
| **Participants** | n = 10  
males=3, females=7  
Mean age 16.5, range 13 to 20 years  
Severity of lung disease; median FEV1 as % predicted 72, median FVC % predicted 53.5  
Patients were recruited as they were admitted with exacerbations of their lung disease with cough productive of tenacious sputum |
| **Interventions** | Pre-treated with nebulised salbutamol 5mg  
Hypertonic saline 6% daily for two days (treatment group)  
Cross over to Isotonic saline daily for two days (control group) |
| **Outcomes**   | Sputum weight  
VAS, feeling of cleared chest |
| **Notes**      | Seven patients were treated for a second block of treatment, but it was not defined who these were. |
| **Allocation concealment** | D |

<table>
<thead>
<tr>
<th>Study</th>
<th>Robinson 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised cross-over trial</td>
</tr>
</tbody>
</table>
| **Participants** | n = 12  
males=9  
females=3  
Mean age = 21.9, range 18 to 28 years SD 3.0  
FEV1 %predicted 60.8 SEM 29.7 range (27 to 112)  
FVC % predicted 77.4 SEM 22.4 |
| **Interventions** | Pre-treated with nebulised salbutamol 5mg  
Hypertonic saline (HS) 7% 7mls single inhalation (treatment group 1)  
Amiloride 3mg (A) single inhalation (treatment group 2)  
HS + A single inhalation (treatment group 3)  
Isotonic saline (IS) single inhalation (control group 1)  
Voluntary cough (VC) single episode All done one week apart (control group 2) |
| **Outcomes**   | Sputum isotope clearance 60 minutes  
Mucociliary clearance rate*  
Change in FEV1 |
| **Notes**      | Patients acted as own controls  
Spirometry measures were taken immediately after inhalation and are not a long term outcome measure. |
| **Allocation concealment** | D |

<table>
<thead>
<tr>
<th>Study</th>
<th>Robinson 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised four way cross-over design</td>
</tr>
</tbody>
</table>
| **Participants** | n = 10  
males=7  
females=3  
Mean age = 22.1, range 19 to 28 SD 3.8  
FEV1 % predicted 52.0% SD 6.7 range 31 to 84% |
| **Interventions** | Pre-treated with nebulised salbutamol 5mg  
Hypertonic saline (HS) 3% single dose (treatment group 1) |
Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Robinson 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised four way cross-over design</td>
</tr>
</tbody>
</table>
| Participants | n = 12  
males=5  
females=7  
Mean age 29.9, range 16 to 46 SD 9.4 |
| Interventions | Pre-treated with terbutaline 1000mcg (turbulhaler)  
Hypertonic 6% 7mls  
Isotonic Saline (0.9%)+ matched voluntary cough  
Mannitol 300mg (encapsulated dry powder)  
Empty capsules with matched voluntary coughs  
All given as a singlre dose |
| Outcomes | Sputum isotope % clearance at 30 minutes  
Sputum isotope clearance at 90 minutes*  
Mucociliary clearance* |
| Notes | Isotope clearance was reported in this paper as occurring at 60 minutes. This is actually the same time period as the 90 minute clearance reported in 1997 paper. The terminology had been changed. |
| Allocation concealment | D |

<table>
<thead>
<tr>
<th>Study</th>
<th>Suri 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised cross-over trial, unblinded</td>
</tr>
</tbody>
</table>
| Participants | n = 48  
Mean age = 12.6 years, range 7.3 to 17 years  
Baseline FEV1 % predicted 47.7%, range 14 to 77% |
| Interventions | Pretreated with bronchodilators. Received HS 7% BD for three months. Crossover after two week washout to RHDNase 2.5mg/day for three months. |
| Outcomes | % change in FEV1 and FVC from baseline |
| Notes |  |
| Allocation concealment | D |

<table>
<thead>
<tr>
<th>Study</th>
<th>Weller 1980</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised parallel group trial</td>
</tr>
</tbody>
</table>
| Participants | n = 56  
males=26  
females=30  
Mean age 10.7, range 6 to 15 years |

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Characteristics of included studies (Continued)

Interventions
Mistabron 20% 3mls bd for eight weeks versus hypertonic saline 7% 3mls bd for eight weeks. No reported pre treatment

Outcomes
PEFR, FVC, V max 50% VC, RV/TLC

Notes
Patients were divided into sputum producers and non sputum producers

Allocation concealment
D

BD: twice a day; CF: cystic fibrosis; FEV1: Forced Expiratory Volume at one second; FVC: Forced Vital Capacity; HS: Hypertonic saline; IS: isotonic saline; MDI: metered dose inhaler; PEFR: peak expiratory flow rate; RV: residual volume; TLC: total lung capacity; VAS: visual analogue scale; VC: Vital capacity.

Characteristics of excluded studies

Genkova 1998
Did not report any results
Did not compare to a control

Hofmann 1997
Study did not measure the effects of hypertonic saline alone, but only with the addition of amiloride

King 1997
In-vitro study only

GRAPHS

Comparison 01 Hypertonic saline (HS) vs Isotonic saline (IS): Percentage change in FEV1

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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</thead>
<tbody>
<tr>
<td>01 Parallel Trial HS vs IS</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
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<tr>
<td>02 Crossover Trial HS vs IS</td>
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<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
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</table>

Comparison 02 Hypertonic saline vs DNase: Change in FEV1

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Parallel Trial HS vs DNAse</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>02 Crossover trial HS vs DNase</td>
<td>2</td>
<td>124</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>-7.36 [-14.08, -0.64]</td>
</tr>
<tr>
<td>03 Improvement in FEV1 &gt; 10%</td>
<td></td>
<td></td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>Subtotals only</td>
</tr>
</tbody>
</table>

Comparison 03 Hypertonic saline (HS) vs Isotonic saline (IS): Percentage change in FVC

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Crossover Trial</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>02 Parallel trial</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
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</tbody>
</table>

Comparison 04 Radiolabelled isotope clearance at 90 minutes

<table>
<thead>
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<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tr>
<td>01 Crossover trial radiolabelled isotope clearance at 90-120 mins</td>
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<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>Comparison</td>
<td>Outcome title</td>
<td>No. of studies</td>
<td>No. of participants</td>
<td>Statistical method</td>
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<td>----------------</td>
<td>---------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>05</td>
<td>02 Parallel Trial radiolabelled isotope clearance at 90 mins</td>
<td>0</td>
<td>0</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
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<tr>
<td></td>
<td>01 Crossover Trial mucociliary clearance as measured as area under the curve</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
</tr>
<tr>
<td></td>
<td>02 Parallel trial mucociliary clearance as measured as area under the curve</td>
<td>0</td>
<td>0</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
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<tr>
<td>06</td>
<td>01 Visual Analogue scale measured at less than 7 days</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
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<tr>
<td>07</td>
<td>01 Cross over trial HS versus DNase</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>08</td>
<td>01 Delivery time minutes HS vs IS</td>
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<td>0</td>
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<tr>
<td></td>
<td>02 Delivery time minutes HS vs DNase</td>
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<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
</tr>
<tr>
<td></td>
<td>03 Delivery time minutes HS vs Mannitol</td>
<td></td>
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<td>Weighted Mean Difference (Fixed) 95% CI</td>
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<tr>
<td>09</td>
<td>01 Acute fall in FEV1 after treatment with HS</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
</tr>
<tr>
<td></td>
<td>02 Increase in cough</td>
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<td></td>
<td>Relative Risk (Fixed) 95% CI</td>
</tr>
</tbody>
</table>

**COVER SHEET**

**Title**
Nebulised hypertonic saline for cystic fibrosis

**Authors**
Wark PAB, McDonald V

**Contribution of author(s)**
Both reviewers selected the trials that were included in this review and each reviewer independently assessed the methodological quality for each trial.
**Issue protocol first published** 1998/3

**Review first published** 1999/2

**Date of most recent amendment** 26 May 2004

**Date of most recent SUBSTANTIVE amendment** 01 November 2002

**What's New**
An additional study - Suri 2001 was found and incorporated in the review. This was a relatively large clinical study comparing hypertonic saline and DNase. Significant changes have been made to the review.
With this update significant changes to style were made particularly in the order of the outcomes and the presentation of the results.

**Date new studies sought but none found** Information not supplied by author

**Date new studies found but not yet included/excluded** Information not supplied by author

**Date new studies found and included/excluded** 01 November 2002

**Date authors' conclusions section amended** Information not supplied by author

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**Cochrane Library number** CD001506

**Editorial group** Cochrane Cystic Fibrosis and Genetic Disorders Group

**Editorial group code** HM-CF
## Graphs and Other Tables

### Fig. 1. Comparison of Hypertonic saline (HS) vs Isotonic saline (IS): Percentage change in FEV1

#### 01.01 Parallel Trial HS vs IS

Review: Nebulised hypertonic saline for cystic fibrosis
Comparison: 01 Hypertonic saline (HS) vs Isotonic saline (IS): Percentage change in FEV1
Outcome: 01 Parallel Trial HS vs IS

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>Isotonic saline</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
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<td>N Mean(SD)</td>
<td>95% CI (%)</td>
<td>95% CI</td>
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<td></td>
</tr>
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<td>25 2.80 (13.00)</td>
<td>100.0 12.20 [ 4.30, 20.10 ]</td>
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<td></td>
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</table>

-100.0 -50.0 0 50.0 100.0
Favours IS Favours HS

### Fig. 2. Comparison of Hypertonic saline (HS) vs Isotonic saline (IS): Percentage change in FEV1

#### 01.02 Crossover Trial HS vs IS

Review: Nebulised hypertonic saline for cystic fibrosis
Comparison: 01 Hypertonic saline (HS) vs Isotonic saline (IS): Percentage change in FEV1
Outcome: 02 Crossover Trial HS vs IS

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>Isotonic saline</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>95% CI (%)</td>
<td>95% CI</td>
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</tbody>
</table>

-100.0 -50.0 0 50.0 100.0
Favours HS Favours IS
### Fig. 3. Comparison 02 Hypertonic saline vs DNase: Change in FEV1

**02.01 Parallel Trial HS vs DNAse**

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>DNase</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td>95% CI (%)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: not applicable

### Fig. 4. Comparison 02 Hypertonic saline vs DNase: Change in FEV1

**02.02 Crossover trial HS vs DNase**

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>DNase</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td>95% CI (%)</td>
</tr>
<tr>
<td>Ballmann 1998</td>
<td>14</td>
<td>14</td>
<td>7.70 (14.00)</td>
<td>9.30 (11.70)</td>
<td>-1.60 [-11.16, 7.96]</td>
</tr>
<tr>
<td>Suri 2001</td>
<td>48</td>
<td>48</td>
<td>3.00 (21.00)</td>
<td>16.00 (26.00)</td>
<td>-13.00 [-22.45, -3.55]</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>62</td>
<td>100.0</td>
<td>-7.36 [-14.08, -0.64]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=2.76 df=1 p=0.10 I²=63.8%
Test for overall effect z=2.15 p=0.03

---

Nebulised hypertonic saline for cystic fibrosis (Review)

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Fig. 5. Comparison 02 Hypertonic saline vs DNase: Change in FEV1

02.03 Improvement in FEV1 > 10%

Review: Nebulised hypertonic saline for cystic fibrosis
Comparison: 02 Hypertonic saline vs DNase: Change in FEV1
Outcome: 03 Improvement in FEV1 > 10%

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>DNase</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td>(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 At three weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ballmann 1998</td>
<td>7/14</td>
<td>6/14</td>
<td>100.0</td>
<td>1.17</td>
<td>[0.52, 2.60]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>14</td>
<td>14</td>
<td>100.0</td>
<td>1.17</td>
<td>[0.52, 2.60]</td>
</tr>
<tr>
<td>Total events: 7 (Hypertonic saline), 6 (DNase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=0.38 p=0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 At three months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suri 2001</td>
<td>14/40</td>
<td>22/40</td>
<td>100.0</td>
<td>0.64</td>
<td>[0.38, 1.06]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>40</td>
<td>40</td>
<td>100.0</td>
<td>0.64</td>
<td>[0.38, 1.06]</td>
</tr>
<tr>
<td>Total events: 14 (Hypertonic saline), 22 (DNase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=1.75 p=0.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 6. Comparison 03 Hypertonic saline (HS) vs Isotonic saline (IS): Percentage change in FVC

03.01 Crossover Trial

Review: Nebulised hypertonic saline for cystic fibrosis
Comparison: 03 Hypertonic saline (HS) vs Isotonic saline (IS): Percentage change in FVC
Outcome: 01 Crossover Trial

<table>
<thead>
<tr>
<th>Study</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>95% CI (%)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Fig. 7. Comparison 03 Hypertonic saline (HS) vs Isotonic saline (IS): Percentage change in FVC**

**03.02 Parallel trial**

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>Isotonic saline</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>95% CI (%)</td>
</tr>
<tr>
<td>01 HS 6% vs IS at 2 weeks</td>
<td>27</td>
<td>8.00 (13.40)</td>
<td>25</td>
<td>2.60 (12.20)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Fig. 8. Comparison 04 Radiolabelled isotope clearance at 90 minutes

**04.01 Crossover trial radiolabelled isotope clearance at 90-120 mins**

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>Isotonic saline</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>95% CI (%)</td>
</tr>
<tr>
<td>01 HS 3-7% vs IS</td>
<td>10</td>
<td>23.80 (12.60)</td>
<td>10</td>
<td>12.70 (4.40)</td>
<td>62.8</td>
</tr>
<tr>
<td>Robinson 1997</td>
<td>12</td>
<td>31.00 (19.00)</td>
<td>12</td>
<td>20.90 (0.08)</td>
<td>37.2</td>
</tr>
<tr>
<td>Robinson 1999</td>
<td>22</td>
<td>20.90 (12.00)</td>
<td>22</td>
<td>20.90 (0.08)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=0.02 df=1 p=0.89 I² =0.0%
Test for overall effect z=3.21 p=0.001
Fig. 9. Comparison 04 Radiolabelled isotope clearance at 90 minutes

04.02 Parallel Trial radiolabelled isotope clearance at 90 mins

Review: Nebulised hypertonic saline for cystic fibrosis
Comparison: 04 Radiolabelled isotope clearance at 90 minutes
Outcome: 02 Parallel Trial radiolabelled isotope clearance at 90 mins

<table>
<thead>
<tr>
<th>Study</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD) 95% CI (%) 95% CI</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0 0 0.0 Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 10. Comparison 05 Mucociliary clearance measured as area under the curve

05.01 Crossover Trial mucociliary clearance as measured as area under the curve

Review: Nebulised hypertonic saline for cystic fibrosis
Comparison: 05 Mucociliary clearance measured as area under the curve
Outcome: 01 Crossover Trial mucociliary clearance as measured as area under the curve

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>Isotonic saline</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD) 95% CI (%) 95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01 HS vs IS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robinson 1996</td>
<td>12 5820.10 (244.50)</td>
<td>12 5943.80 (273.30)</td>
<td>8.2 -123.70 [-331.18, 83.78 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robinson 1997</td>
<td>10 5675.00 (69.60)</td>
<td>10 5895.00 (72.30)</td>
<td>91.8 -220.00 [-282.20, -157.80 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>22 100.0 -212.06 [-271.64, -152.48 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=0.76 df=1 p=0.38 I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=6.98 p&lt;0.00001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-1000.0 -500.0 0 500.0 1000.0
Favours HS Favours IS
**Fig. 11. Comparison 05 Mucociliary clearance measured as area under the curve**

**05.02 Parallel trial mucociliary clearance as measured as area under the curve**

Review: Nebulised hypertonic saline for cystic fibrosis
Comparison: 05 Mucociliary clearance measured as area under the curve
Outcome: 02 Parallel trial mucociliary clearance as measured as area under the curve

<table>
<thead>
<tr>
<th>Study</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>95% CI (%)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: not applicable

-10.0 -5.0 0 5.0 10.0
Favours HS Favours IS

**Fig. 12. Comparison 06 Visual Analogue scale, feeling of cleared chest**

**06.01 Visual Analogue scale measured at less than 7 days**

Review: Nebulised hypertonic saline for cystic fibrosis
Comparison: 06 Visual Analogue scale, feeling of cleared chest
Outcome: 01 Visual Analogue scale measured at less than 7 days

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>Isotonic saline</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>95% CI (%)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>01 HS 6% vs IS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eng 1996</td>
<td>27</td>
<td>25</td>
<td>1.17 (1.25)</td>
<td>81.8</td>
<td>0.88 [0.19, 1.57]</td>
</tr>
<tr>
<td>Redler 1996</td>
<td>10</td>
<td>10</td>
<td>0.10 (1.95)</td>
<td>18.2</td>
<td>1.40 [-0.07, 2.87]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>37</td>
<td>35</td>
<td>0.97 [0.35, 1.60]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=0.39 df=1 p=0.53 I² =0.0%
Test for overall effect z=3.05  p=0.002

-10.0 -5.0 0 5.0 10.0
Favours IS Favours HS
Fig. 13. Comparison 07 Frequency of exacerbations

07.01 Cross over trial HS versus DNase

Review: Nebulised hypertonic saline for cystic fibrosis
Comparison: 07 Frequency of exacerbations
Outcome: 01 Cross over trial HS versus DNase

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>DNase</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun 2001</td>
<td>15/45</td>
<td>18/45</td>
<td>0.83 [ 0.48, 1.44 ]</td>
<td>100.0</td>
<td>0.83 [ 0.48, 1.44 ]</td>
</tr>
</tbody>
</table>

Favours HS  Favours DNase

Fig. 14. Comparison 08 Delivery time

08.01 Delivery time minutes HS vs IS

Review: Nebulised hypertonic saline for cystic fibrosis
Comparison: 08 Delivery time
Outcome: 01 Delivery time minutes HS vs IS

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>Isotonic saline</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 15. Comparison 08 Delivery time

08.02 Delivery time minutes HS vs DNase

Review: Nebulised hypertonic saline for cystic fibrosis
Comparison: 08 Delivery time
Outcome: 02 Delivery time minutes HS vs DNase

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>DNase</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ballmann 1998</td>
<td>14</td>
<td>14</td>
<td>31.00 [ 24.44, 37.56 ]</td>
<td>100.0</td>
<td>31.00 [ 24.44, 37.56 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>14</td>
<td>14</td>
<td>31.00 [ 24.44, 37.56 ]</td>
<td>100.0</td>
<td>31.00 [ 24.44, 37.56 ]</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=9.26  p&lt;0.00001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-100.0 -50.0 0 50.0 100.0
Favours HS  Favours DNase
**Fig. 16. Comparison 08 Delivery time**

08.03 Delivery time minutes HS vs Mannitol

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>Mannitol</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson 1999</td>
<td>12</td>
<td>12</td>
<td>6.20 (1.20)</td>
<td></td>
<td>12.30 (1.80)</td>
</tr>
</tbody>
</table>

Study Hypertonic Mannitol Weighted Mean Difference (Fixed) Weight Weighted Mean Difference (Fixed)

Robinson 1999 12 6.20 (1.20) 12 12.30 (1.80) 100.0 -6.10 [ -7.32, -4.88 ]

**Fig. 17. Comparison 09 Adverse events**

09.01 Acute fall in FEV1 after treatment with HS

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>Isotonic saline</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson 1999</td>
<td>12</td>
<td>12</td>
<td>5.80 (4.20)</td>
<td></td>
<td>0.60 (9.34)</td>
</tr>
</tbody>
</table>

01 Acute fall in FEV1 HS vs IS

01 Increase in cough HS vs IS

02 Increase in cough HS versus DNase

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>Isotonic saline</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suri 2001</td>
<td>13/45</td>
<td>17/45</td>
<td>1.00</td>
<td>100.0</td>
<td>0.76 [0.42, 1.38 ]</td>
</tr>
</tbody>
</table>

**Fig. 18. Comparison 09 Adverse events**

09.02 Increase in cough

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>Isotonic saline</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
</table>

02 Increase in cough HS versus DNase

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertonic saline</th>
<th>Isotonic saline</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
</table>

Suri 2001 13/45 17/45 100.0 0.76 [0.42, 1.38 ]