



Care of Patients With Pulmonary Disorders

Mucoactive agents for adults with acute lung conditions: A systematic review

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ABSTRACT

Background and objectives: Inhaled mucoactive agents are used to enhance airway clearance, however efficacy and safety are unclear in adults with acute respiratory conditions.

Methods: We systematically reviewed randomized controlled trials assessing respiratory function; safety; length of stay (LOS); mucus; radiology; and oxygenation.

Results: No adverse events were reported for dornase alfa ($n = 63$), N-acetylcysteine (NAC, $n = 50$), ambroxol ($n = 140$), hypertonic saline ($n = 33$), heparin ($n = 384$), mannitol ($n = 20$) or isotonic saline. During invasive ventilation, NAC, dornase alfa and saline had no effect on mucus. Postoperatively, mucus characteristics improved with NAC ($n = 10$). Ambroxol lowered LOS (mean difference 4 days) and halved complications following lung carcinoma resection ($n = 140$). Heparin improved ventilator-free days ($n = 130$, mean difference 3.9–4.6) and intensive care LOS ($n = 223$, 3.2 days), but not ventilator-acquired pneumonia.

Conclusion: Dornase alfa, hypertonic saline and NAC were ineffective for atelectasis/mucus plugging while intubated. More data are required to support using NAC, ambroxol and heparin during acute illness.

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Introduction

During episodes of infection, the human airway responds with an increase in mucus production and release of inflammatory material. This can cause mucus retention, plugging, and structural change to the airways.¹ Mucoactive agents are medications that affect

mucociliary clearance (MCC) and/or mucus characteristics, thereby promoting airway clearance.^{2,3}

Use of inhaled mucoactive agents has been described in the acute management of abnormal mucus production, when MCC or cough is compromised,⁴ including acute respiratory failure and postoperative care.⁵ Invasively ventilated patients are at a high risk of respiratory compromise due to mucus plugging and atelectasis, and have been shown to have abnormally viscous mucus.⁶ Postoperative pulmonary complications are also prevalent following general anesthesia, which can reduce lung volumes and compromise MCC, increasing the risk of infection and prolonged hospital stay.⁷

A range of mucoactive agents are used in clinical practice. Expectorants like isotonic (IS) and hypertonic saline (HS) act by increasing mucosal water volume, stimulating cough,¹ and facilitating efficient expectoration via maintenance of the airway surface liquid layer, decreasing mucus adhesiveness.² Mucolytics such as N-acetylcysteine (NAC), dornase alfa and heparin⁸ break down inflammatory material by degrading the biophysical properties of mucus, reducing viscosity, thereby improving airway clearance.^{1,2} Mucokinetic agents promote airway clearance by enhancing ciliary beat frequency, loosening adherent mucus from airway walls and increasing expiratory flow with cough.^{1,2} In particular, ambroxol is thought to stimulate surfactant

Abbreviations: NSCLC, non-small cell lung cancer; LOS, length of stay; IS, isotonic saline; NAC, N-acetylcysteine; AEs, adverse events; HS, hypertonic saline; MCC, mucociliary clearance; CF, cystic fibrosis; FER, forced expiratory ratio; PF, partial pressure of oxygen / fraction of inspired oxygen ratio; COPD, chronic obstructive pulmonary disease; Vt, tidal volume; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; CI, confidence interval; SD, standard deviation; RCT, randomized controlled trial; PEEP, positive end expiratory pressure, mmHg, millimeters of mercury; ml, milliliters; kg, kilograms; SpO₂, peripheral capillary oxygen saturation; ICU, intensive care unit; PLT, platelets; ARDS, acute respiratory distress syndrome; PaCO₂, partial pressure of carbon dioxide; RR, risk ratio; QOL, quality of life

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production and reduce mucus viscosity.⁹ Due to variances in their modes of action, not all mucoactive agents should be treated alike.

Current literature regarding the use of mucoactive agents is primarily in chronic respiratory disease. There is established evidence in cystic fibrosis (CF),^{10–12} and a recent systematic review has shown that mannitol, HS and IS may also be effective in chronic non-CF bronchiectasis.¹³ The short-term role of inhaled mucoactive agents in acute care is not clear,^{14,15} therefore the aims of this systematic review were to determine the impact of inhaled mucoactive agents on 1) Respiratory or ventilatory function; 2) Healthcare utilization; 3) Mucus characteristics; 4) Oxygenation and radiological findings; 5) Patient-reported symptoms or quality of life (QOL); and 6) Adverse events (AEs) in acute lung conditions.

Methods

Protocol and eligibility

This was a systematic review with a review question, search strategy and protocol that were defined and published a priori (Prospero, #CRD42014015496, dated 15/12/14). Parallel and crossover randomized controlled trials (RCTs) in adults were included. Trials published in a language other than English were excluded unless an English abstract was available. Participants had a diagnosis of any acute lung condition, including respiratory failure leading to invasive ventilation, atelectasis and postoperative pulmonary complications. Trials on participants with a principal diagnosis of chronic respiratory disease (e.g. chronic obstructive pulmonary disease (COPD), CF, asthma or non-CF bronchiectasis) were reported separately.¹³ Respiratory comorbidity is however common in both critical care¹⁶ and acute care settings,^{17,18} therefore trials including patients with a pre-existing diagnosis of chronic respiratory disease were not excluded, provided participants were receiving treatment in the acute setting. We excluded CF, as we deemed there to be sufficient evidence to guide mucoactive agent use in this cohort.¹

Inhaled mucoactive medications using any device at any dose, frequency or duration were compared to usual care, no mucoactive agent, placebo, comparison or control. Each medication was analyzed separately. Studies combining mucoactive agents with other treatments were included. Mucoregulatory agents and cough-clearance promoters³ such as anti-inflammatories, antibiotics, anticholinergic medications and bronchodilators were excluded, as they do not have a direct impact on airway mucus.¹⁹ Surfactants were excluded due to variability in preparation.²⁰ Outcomes included respiratory or ventilatory function; health related QOL or patient-reported symptoms; healthcare utilization, including LOS, readmissions and duration of medical supports; exacerbations; MCC and mucus characteristics, such as weight, colour or viscosity; oxygenation; radiological findings; inflammation; and AEs, such as mortality, bronchospasm, hemoptysis or hypoxemia.

Sources

We systematically searched key medical, nursing and allied health databases of Medline, Embase, CINAHL and CENTRAL using individual strings, each run through a precision hedge by a senior librarian (LR) (e-Method 1). Our search included terms for common respiratory diagnoses (e.g. respiratory infection), pathophysiology (e.g. sputum), mucoactive agents (e.g. saline solution) and intervention (e.g. airway clearance). The initial search was dated 04/03/15, repeated on 31/03/16 and 02/01/2018. Citation tracking of included trials and relevant reviews was completed. Grey literature searching was performed dated to 02/01/2018, including trial registrations on the Australian New Zealand Clinical Trials Registry and Clinicaltrials.gov, and abstracts from the American Thoracic Society International

Conference, European Respiratory Society and British Thoracic Society Annual Congresses (e-Method 2).

Data collection and risk of bias

Authors BT and RS/CL examined title and abstract to determine if inclusion criteria were met. Trials that met criteria or were unclear were examined in full text. Excluded trials were recorded with reason(s) for exclusion (Fig. 1; Supplementary Material 2). Data were extracted using standardised forms. Risk of bias was assessed by BT and CL using The Cochrane Collaboration's Risk of Bias Assessment Tool²¹ (Fig. 2); a seven-component tool analyzing selection, performance, detection, attrition, and reporting bias, categorized into high, low or unclear risk. If disagreement arose, a third investigator (AH) was included until consensus was reached.

Synthesis

When possible, we used data from intention to treat analyses. Dichotomous variables were expressed as risk ratios (RR) or risk difference with 95% confidence intervals (CI). For continuous data we recorded either the mean change from baseline or the mean post-intervention values \pm standard deviation (SD). We reported outcomes as mean differences or standardized mean differences with 95%CI. Where meta-analysis was possible this was stated, including the outcome(s) and method used. Meta-analysis of heparin on ICU LOS and invasive ventilation days included approximated data (median = mean, SD = IQR/1.35).²¹ Where not possible, a narrative appraisal of each trial and outcome was presented.

Results

After removal of duplicates, 9,636 citations were screened by title and abstract. After screening, 227 full-text articles were reviewed, of which 10 trials were included (Fig. 1). Trial participants included critically ill and acute medical, surgical and trauma inpatients.^{22–31} Dornase alfa was investigated in two studies,^{22,23} NAC in two,^{24,26} heparin in four,^{27,29–31} and HS,²² mannitol²⁸ and ambroxol²⁵ once each. Isotonic saline was used in seven trials as a control agent.^{22–24,26,27,29,30} There were eight parallel and two crossover RCTs,^{24,28} all of which collected prospective, trial specific data. One conference abstract was included.²⁸ Sample sizes ranged from 11 to 214, and detailed characteristics are presented in e-Table 1. Raw data are presented in e-Table 2.

All trials were conducted in the acute care setting. Participants with COPD exacerbations were included in two trials, affecting 2/50 (4%) participants in one heparin trial,²⁹ and 1/30 (3%) in one dornase alfa trial.²³ In addition, COPD was a reported comorbidity in three trials, affecting 45/214 (21%)²⁷ and 3/40 (7.5%)³⁰ participants in two heparin trials, and 30% of participants in the NAC trial.²⁶ There were no significant between-group differences in the proportion of participants with COPD in any trial.

Only three trials reported blinding of participants, personnel and assessors,^{22,23,27} with the remaining seven at risk of performance and/or detection bias.^{24–26,28–31} Two trials were at a high risk of attrition bias due to high dropout rates²³ and early trial cessation,²⁷ and we deemed the conference abstract to be at a high risk of reporting bias²⁸ (Fig. 2). Four trials could be included in meta-analysis, with a narrative synthesis also reported for these and the other six trials.

Respiratory function and ventilation

Overall, inhaled mucoactive agents failed to improve this outcome. Five days of dornase alfa used for atelectasis during invasive ventilation did not change tidal volume (Vt) or lung compliance

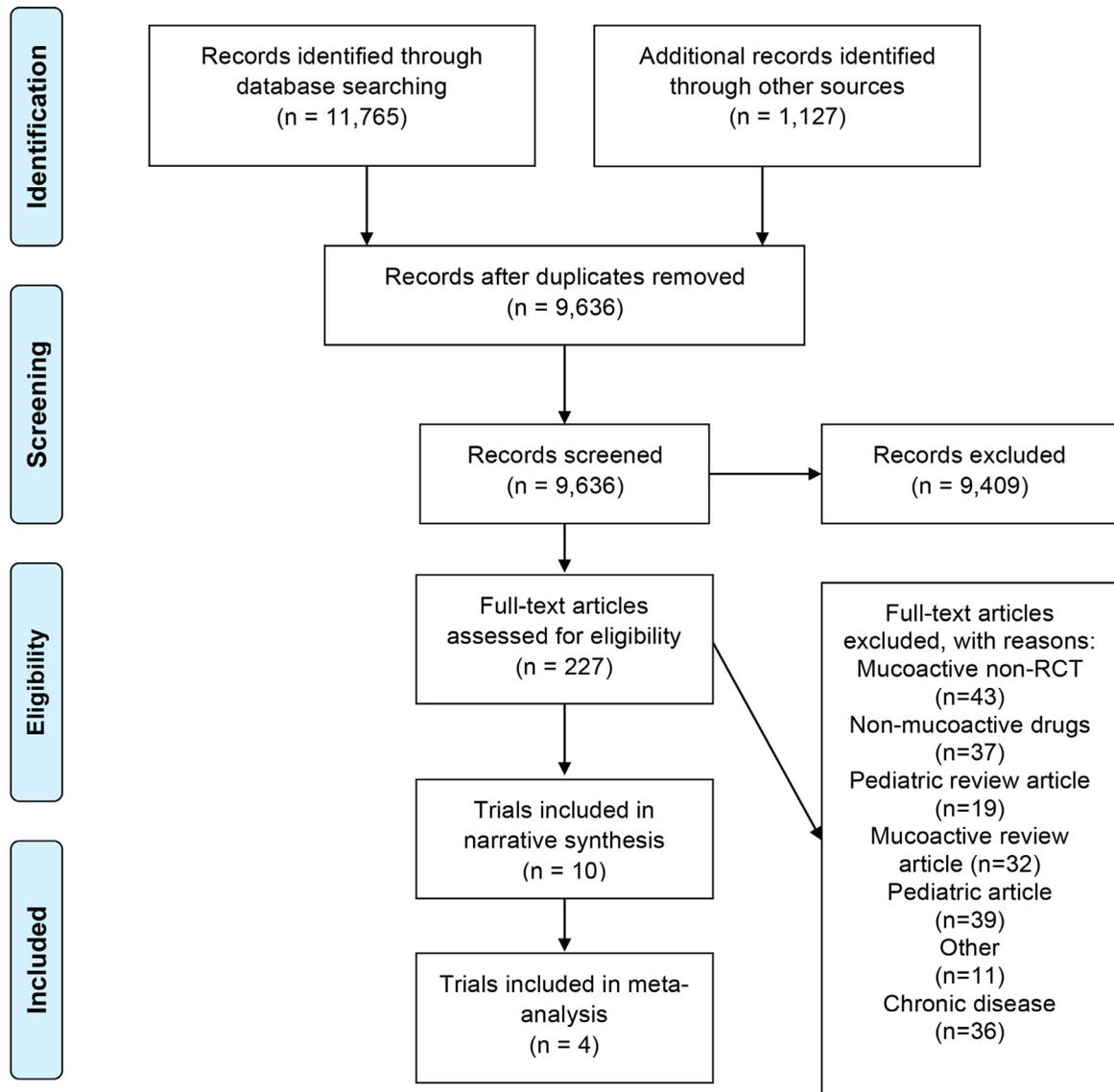


Fig. 1. PRISMA® diagram of study selection.

compared with IS ($n = 30$),²³ nor did it affect positive end expiratory pressure (PEEP) ($n = 63$).^{22,23} A single dose of 160–320 mg mannitol during invasive ventilation ($n = 20$) caused no change to airway resistance up to 60 minutes following inhalation, nor did placebo.²⁸ Similarly, one day of NAC (or IS) during invasive ventilation ($n = 40$) failed to change airway pressures up to 24 h from baseline.²⁶

When used perioperatively during cardiac surgery in those at risk of lung injury, heparin lowered mean postoperative alveolar dead space fraction (0.11 ± 0.07 vs. 0.16 ± 0.08 , $p < 0.05$) and Vt (7.9 ± 1.3 vs. 9.0 ± 1.1 ml/kg, $p < 0.01$) while increasing end-tidal carbon dioxide (CO_2) (35.3 ± 3.3 vs. 32.9 ± 2.4 mmHg, $p < 0.05$) over IS.³⁰ This was not sustained 1–4 h following surgery. Respiratory rate and arterial pressure of CO_2 (PaCO_2) were similar between groups. Neither heparin or IS during invasive ventilation in critical illness led to a significant change in PaCO_2 , Vt, minute ventilation, respiratory rate, peak inspiratory pressure or PEEP over seven days ($n = 50$).²⁹

Adverse events

The use of mucoactive agents in acute lung conditions did not increase the risk of AE. One of two trials reported on AEs with NAC

over one day during invasive ventilation ($n = 40$).²⁶ Participants had a diagnosis of pneumonia or sepsis, and in-hospital mortality rate was 50% (NAC) and 35% (IS). No AEs such as bronchospasm, fever or rhinorrhea were reported following a NAC dose of 2%, in light of a pilot trial reporting bronchospasm with 3%.²⁶

Two trials screened for AEs during daily dornase alfa use over one to seven days of invasive ventilation ($n = 63$).^{22,23} No AEs were reported, including wheeze and hypoxemia. Meta-analysis revealed that all-cause mortality was no different at day 5 (Fig. 3) or for the duration of follow-up (day 7, e-Fig. 1) compared with IS. Twice daily HS (7%) and IS were compared during invasive ventilation with atelectasis over seven days or until resolution ($n = 33$).²² No AEs were attributed to either medication.

Four trials of inhaled heparin ($n = 313$) used during invasive ventilation either in the intensive care unit (ICU)^{27,29,31} or operating theatre³⁰ were analyzed. The only significant AE was a fall in mean platelet count (PLT) in acute respiratory distress syndrome (ARDS) compared to usual care (217.6 ± 42.1 vs. 241.8 ± 47.4 , $p = 0.018$) ($n = 80$).³¹ Other AEs were unchanged, including mortality, ventilator-associated complications, coagulation, hemoptysis, multi-organ failure, blood product or vasoactive medication requirements and

| | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|-----------------|---|---|---|---|--|--------------------------------------|------------|
| Bandeshe 2016 | + | + | + | + | - | + | + |
| Chan 2012 | + | ? | - | - | + | - | - |
| Dixon 2010 | + | + | + | ? | + | + | - |
| Dixon 2016 | + | + | + | ? | + | ? | + |
| Gallon 1996 | + | ? | - | ? | + | + | + |
| Masoompour 2015 | + | + | - | ? | + | ? | + |
| Saleh 2017 | + | ? | ? | ? | ? | + | + |
| Wang 2015 | + | ? | - | ? | + | + | + |
| Youness 2012 | + | ? | + | + | + | + | + |
| Zitter 2013 | + | ? | + | + | - | + | - |

Fig. 2. Assessment of risk of bias: low risk: +, high risk: -, unclear risk: ?.

protocol defined withholding of anticoagulants. Meta-analysis from two trials of heparin delivered during invasive ventilation ($n=223$)^{27,31} revealed no significant difference in ICU mortality

(Fig. 4), PLT or activated partial thromboplastin time (e-Figs. 2.1 and 2.2) in those diagnosed with, or at risk of ARDS and/or pneumonia.

Healthcare utilization

Benefits of inhaled mucoactive agents on healthcare utilization were evident for ambroxol in the post-surgical setting, and heparin during invasive ventilation. Ambroxol pre and post surgical resection of non-small cell lung cancer (NSCLC) ($n=140$) shortened mean length of hospital stay by four days compared with no mucoactive agent (7.77 ± 2.52 vs. 11.62 ± 3.99 , $p < 0.05$).²⁵ Heparin during invasive ventilation in ARDS ($n=80$)³¹ significantly lowered mean ventilation days and ICU LOS compared with usual care (9.6 ± 13.5 vs. 13.5 ± 3.1 ; 12.7 ± 4.3 vs. 17.7 ± 3.7 days, $p < 0.001$). Meta-analysis ($n=223$)^{27,31} revealed no difference in invasive ventilation duration (e-Fig. 3), but a reduction in ICU LOS (mean difference -3.20 days, 95%CI -4.61 to -1.79), with marked heterogeneity ($I^2=91\%$) (e-Fig. 4). Similarly, up to 14 days of heparin during invasive ventilation due to critical illness improved ventilator-free days among survivors at 28 days (mean difference 4.6 days, 95%CI 0.9–8.3, $p=0.02$), but did not significantly alter ICU LOS (mean difference -4.7 days, 95%CI -11.4 to 2.1, $p=0.2$) or hospital LOS (mean difference 3 days) over IS ($n=50$).²⁹ Intraoperative heparin did not improve invasive ventilation duration, LOS, return to theatre or readmission up to 30 days post cardiac surgery compared with IS ($n=40$).³⁰

Daily dornase alfa administration during invasive ventilation with atelectasis was measured in two trials ($n=63$).^{22,23} Results were conflicting, with one trial reporting a significant increase in the likelihood of extubation over IS at day one (14% vs 7% extubated),²³ with the other finding no difference in the likelihood of extubation between IS (54%), HS (45%) or dornase alfa (63%) after seven days.²² Compared with IS, meta-analysis revealed no increased likelihood of extubation with dornase alfa over five days (Day 1 and 5: Figs. 5.1 and 5.2. Days 2, 3, 4: e-Figs. 5.1–5.3).

Mucus characteristics

Benefits for this outcome were inconsistent across mucoactive agents. After two days of use following thoracic or abdominal surgery ($n=10$), NAC increased mean mucus weight from 2.65 ± 3.47 g to 7.50 ± 6.29 g, while IS had no effect (3.45 ± 2.16 to 3.55 ± 2.99 g).²⁴ Post-surgery, NAC, but not IS, improved viscosity after two days ($n=10$).²⁴ Between-group significance was not stated in either instance. During invasive ventilation ($n=40$), neither NAC nor IS lowered mucus density after three doses over 24 h.²⁶ Heparin during invasive ventilation in critical illness led to no significant changes in respiratory microbiology at 14 days compared with IS ($n=50$),²⁹ nor was there any difference in respiratory microorganisms, need for suction or secretion volume after initiation of invasive ventilation compared with IS or usual care ($n=214$).²⁷

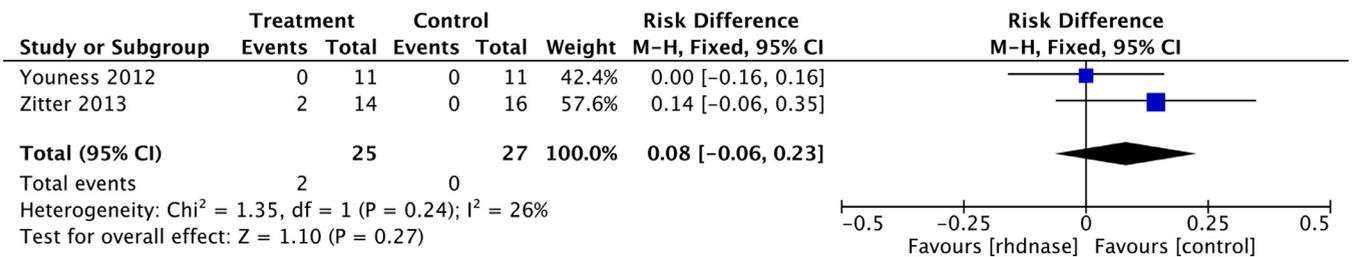


Fig. 3. Dornase alfa in atelectasis: Meta-analysis for likelihood of mortality day 5.

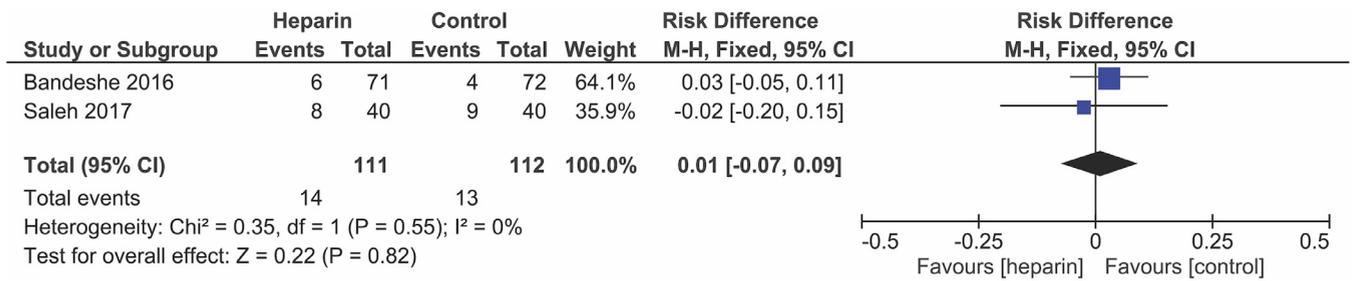


Fig. 4. Heparin during mechanical ventilation: Meta-analysis of ICU mortality.

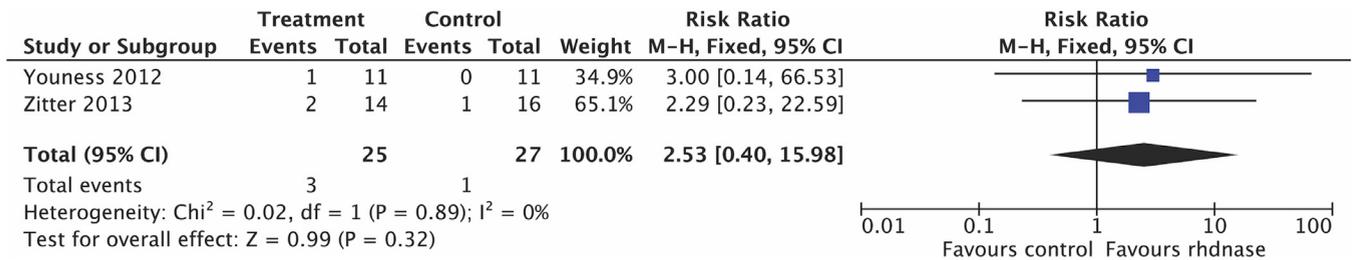


Fig. 5.1. Dornase alfa in atelectasis: Meta-analysis for likelihood of extubation day 1.

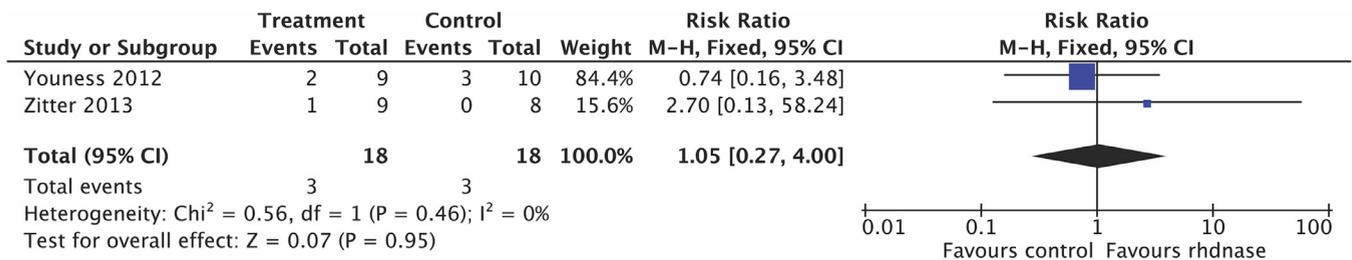


Fig. 5.2. Dornase alfa in atelectasis: Meta-analysis for likelihood of extubation day 5.

Auscultation, radiology and inflammation

Overall, there lacked evidence for benefit to these outcomes with any mucoactive agent. Three doses of NAC during invasive ventilation ($n=40$) reduced rhonchi prevalence from 70% to 25% at 24 h ($p=0.002$). Normal saline also effectively reduced rhonchi by 30% ($p=0.045$).²⁶ After five to seven days of dornase alfa administration during invasive ventilation with atelectasis ($n=63$), chest x-ray scores did not change,^{22,23} nor were there differences between IS or HS. After four days of use during invasive ventilation, heparin had no effect on inflammatory markers via pulmonary lavage over IS ($n=50$).²⁹

Oxygenation

The impact on oxygenation was inconsistent across trials and agents. Two trials of dornase alfa in atelectasis during invasive ventilation revealed conflicting results ($n=63$).^{22,23} In one trial, mean partial pressure of oxygen/fraction of inspired oxygen (PF) ratio was significantly better at 399 mmHg post dornase alfa at day five, compared to 256 mmHg post IS ($p=0.03$).²³ In another, there was no mean difference between groups over one to seven days (day five: 236 ± 100 dornase alfa; 191 ± 53 HS; 301 ± 60 mmHg IS).²² After two days of NAC post thoracic or abdominal surgery ($n=10$), mean SpO₂ improved from 91.6 ± 3.75% to 93.96 ± 2.67% ($p < 0.001$). There was no change with IS (93.08 ± 3.23 to 93.35 ± 3.64%), but between-group significance was not reported.²⁴ One day of NAC during invasive ventilation ($n=40$) improved mean SpO₂ at 12 h after three doses

(93.8 ± 2.7 to 95.1 ± 2.6%), but this was no better than IS (94.0 ± 2.2 to 93.9 ± 2.5%) ($p=0.30$).²⁶

A single dose of either 160 mg or 320 mg mannitol caused no change to SpO₂ during invasive ventilation compared to placebo ($n=20$).²⁸ One week of heparin use in polytrauma/ARDS improved PF ratio compared with control (231.1 ± 42.7 vs. 203.6 ± 45.9 mmHg, $p < 0.001$) ($n=80$).³¹ When used intraoperatively during cardiac surgery ($n=40$), heparin did not improve PF ratio compared with placebo 2–4 h postoperatively,³⁰ nor did it change PF ratio or oxygenation index over seven days during invasive ventilation compared with IS ($n=50$).²⁹

Postoperative complications, disease severity and symptoms

There were benefits for mucoactive agents in postoperative cohorts only, especially in those spontaneously ventilating. Following surgical resection of NSCLC ($n=140$), ambroxol reduced total postoperative complications by 27%, compared with control (13%). There were fewer pulmonary-specific complications including invasive ventilation, atelectasis, respiratory infection, prolonged intercostal catheter air leak and/or pleural effusion (8%, control 19%). Cardiac complications were no different between groups.²⁵ Two days of NAC following thoracotomy or laparotomy improved ease of mucus expectoration over IS by 3.75 cm (visual analogue scale, $n=10$). Isotonic saline was not effective (0.27 cm), however between-group significance was not stated.²⁴

One week of heparin during invasive ventilation in ARDS improved mean lung injury severity scores (1.82 ± 0.66) compared with usual care (2.35 ± 0.35) ($p < 0.001$, $n=80$).³¹ Heparin during

invasive ventilation also lowered the need for nitric oxide by 19% over IS (RR 0.8, $p = 0.05$, $n = 50$),²⁹ but did not decrease the need for tracheostomy, improve renal failure-free days, affect requirement for antibiotics, steroids, and nebulized therapies, or reduce acute lung injury ($n = 264$).^{27,29} Ventilator-acquired pneumonia rates and Sequential Organ Failure Assessment scores were no different between groups ($n = 214$).²⁷

A single dose of 320 mg mannitol in participants with mucus retention during invasive ventilation ($n = 20$) caused more mean coughs than placebo (18 ± 14 vs. 4 ± 7 , $p = 0.02$). A lower dose of 160 mg caused no increase in cough number (15 ± 12 vs. 7 ± 10 , $p = 0.3$).²⁸ Dornase alfa did not reduce the need for bronchoscopy over HS or IS ($n = 63$),^{22,23} nor did it alter the need for bronchodilators or additional mucoactive agents during invasive ventilation over IS ($n = 30$).²³ This finding is consistent with the lack of conclusive benefit seen in all other outcomes.

Discussion

Inhaled mucoactive agents caused no significant AEs in postoperative^{24,25} or ventilated participants.^{22,23,26–31} Postoperative pulmonary complications and LOS improved with ambroxol following NSCLC surgery,²⁵ while mucus characteristics improved with NAC post thoracic and/or abdominal surgery.²⁴ Oxygenation, radiological markers, ventilation settings, airway physiology and mucus characteristics all remained unchanged with dornase alfa,^{22,23} NAC,²⁶ HS,²² mannitol²⁸ and IS during invasive ventilation. Heparin failed to have an impact on ventilator-acquired pneumonia,²⁷ but did improve ventilator-free days,^{29,31} intraoperative ventilation characteristics,³⁰ ICU LOS, oxygenation and lung injury severity³¹ (Table 1).

Healthcare utilization

Both ambroxol²⁵ and heparin³¹ appeared to lower acute LOS, with ambroxol also reducing postoperative pulmonary complications, and heparin leading to inconsistent benefits to ventilation duration.^{27,30,31} Fast-track surgical management of NSCLC alone reduces LOS,³² and it appears ambroxol may help further. A lack of consensus regarding heparin dose and frequency³³ was again observed in this review^{27–31}; therefore a uniform approach is needed for future trials. Dornase alfa failed to have any impact on clinical outcomes,^{22,23} therefore based on these results and significant cost,³⁴ use outside of CF is still not supported.¹²

Table 1
Summary of benefit. I+V: intubated and mechanically ventilated; HS: hypertonic saline, IS: isotonic saline, NAC: N-acetylcysteine, NSCLC: non-small cell lung cancer; #: summary of findings adapted from the Cochrane Handbook for Systematic Reviews,¹⁷ benefit = one or more trials show positive results in >1 outcomes; *: based on trial methodology and/or availability of results.

| | Potential benefit# | Unclear* | No benefit |
|---|---|------------------------|--|
| Atelectasis during mechanical ventilation | | | HS ²² IS ^{22,23} Dornase alfa ^{22,23} |
| Thoracic/abdominal surgery Critical care, mechanical ventilation | NAC ²⁴ Heparin ^{29–31} | Mannitol ²⁸ | IS ²⁴ IS ^{26,27,29} |
| Intra operative cardiac surgery NSCLC | Heparin ³⁰ Ambroxol ²⁵ | | NAC ²⁶ Heparin ²⁷ IS ³⁰ |

Physiology and pathology

When combined with the Active Cycle of Breathing Technique, NAC was effective postoperatively,²⁴ improving symptoms, oxygenation and mucus characteristics. However during invasive ventilation, NAC failed to improve mucus density, oxygenation or airway pressures.²⁶ Mucus characteristics may not be sensitive enough to reflect improvement in clinical outcomes,³⁵ therefore application in the postoperative setting should be considered with this in mind. When used during invasive ventilation with atelectasis, both dornase alfa and HS had no effect on radiological measures, oxygenation or respiratory physiology.^{22,23} Similar findings have been demonstrated in pediatrics with tracheomalacia,³⁶ bronchiolitis^{37,38} and during invasive ventilation.^{39,40} This is in contrast to case studies in adults^{1,2,19} and pediatric atelectasis,⁴¹ demonstrating resolution of atelectasis and mucus impaction following dornase alfa use. We recommend careful selection of sensitive outcomes in future trials.

Safety

There were no AEs reported with the use of any agent in acute care, which is consistent with conclusions drawn from a recent review in chronic respiratory conditions, with the exception of dornase alfa in non-CF bronchiectasis, which was detrimental.¹³ Isotonic saline was used as a control on seven occasions,^{22–24,26,27,29,30} demonstrating a good safety profile, while having no impact on outcomes, therefore we believe IS may be a suitable control agent for future trials. Apparent safe delivery of mannitol during invasive ventilation paves the way for future interventional trials.²⁸

Limitations

Limitations of studies in this review included susceptibility to performance bias due to lack of blinding^{24–26,28–31} high dropout rates²³ and inadequately described power calculations.^{24,25,28,31} Two trials did not mandate mucus burden,^{25,26} while four trials utilized heparin prophylactically.^{27,29–31} Future trials should target patients with objective evidence of abnormal mucus. Inhalation device and technique must be specifically tailored to each medication, affecting deposition and efficacy, especially in invasive ventilation^{42,43} or tracheostomy cohorts.⁴⁴ Only five trials^{24,27–30} adequately described device and particle size estimate. We recommend future trials report this to improve repeatability and external validity.

Limitations of this review include small sample sizes and the ability to perform meta-analysis from only four trials on five occasions due to the variety of agents and heterogeneity of outcomes. This renders assessment for publication bias by traditional methods unsuitable.⁴⁵ Small sample sizes, especially if underpowered, can produce false-positive results.⁴⁶ This limits our conclusions and must be taken into account when applying these results clinically. The absence of AEs should not be interpreted as definitive medication safety, especially as some participants were sedated and ventilated.^{22,23,26–31}

Conclusion

The use of inhaled mucoactive agents led to no significant AEs in invasively ventilated or postoperative participants with acute lung conditions. Dornase alfa,^{22,23} HS,²² IS^{22,23,26} and NAC²⁶ were ineffective in treating mucus plugging and atelectasis during invasive ventilation. Heparin was ineffective for ventilator-acquired pneumonia,²⁷ but did improve ventilator-free days,²⁹ ICU LOS, oxygenation and lung injury severity when used prophylactically during invasive ventilation.³¹ Promising results of NAC²⁴ and ambroxol²⁵ in the postoperative setting require further examination. It appears that mannitol can be delivered

safely during invasive ventilation, although clinical efficacy needs to be evaluated.²⁸ Each inhaled mucoactive agent should be considered individually in the presence of differing acute respiratory conditions, and future research should target participants who have mucus abnormalities causing respiratory compromise.

Declarations of interest

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Supplementary data

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