Nebulized furosemide for the management of dyspnea: does the evidence support its use?

CRD summary
The authors concluded that nebulized furosemide appeared to have a positive effect on dyspnoea and physiological measurements, but the conclusions were limited by the small scale or methodological limitations of many included studies. Given the unclear quality of the included studies, the reliability of the authors' conclusions is unclear and their caution is justified.

Authors' objectives
To evaluate the effectiveness of nebulized furosemide in the management of dyspnoea.

Searching
MEDLINE, EMBASE, CINAHL and the Internet were search for articles in English between 1988 and 2006. Search terms were reported. Bibliographies of identified articles were searched.

Study selection
Randomised or non-randomised clinical or experimental studies of nebulized furosemide in the management of dyspnoea in adults were eligible for inclusion.

Included studies compared nebulized furosemide in doses ranging from 10mg to 100mg to saline, salbutamol, metaproterenol, solvent, vehicle, bumetanide, matched placebo, amiloride, ethacrynic acid, or polyethylene glycol and tromethamol. The majority of included studies were of asthmatic participants investigating acute asthma or asthma experimentally-induced using a variety of mediums. Studies of healthy adults and patients with cancer or chronic obstructive pulmonary disease (COPD) were also included. Outcomes reported in the included studies were a variety of physiological changes; most common were peak expiratory flow rate, forced expiratory volume in one second (FEV₁) and dyspnoea symptoms.

The authors did not state how the study selection was performed or how many reviewers performed the study selection.

Assessment of study quality
The authors did not state that they assessed study validity.

Data extraction
The authors did not state how the data were extracted for the review.

Methods of synthesis
The studies were combined in a narrative synthesis, with results discussed separately for each of the participant groups.

Results of the review
Forty-two studies were included for the review: 20 randomised controlled trials (RCT, n=462 participants), 19 randomised controlled crossover trials (RCCT, n=238 participants), one open label clinical trial (n=15 participants), and two case studies (n=10 participants).

Asthma: In patients with acute asthma, nebulized furosemide was associated with a significant increase of 28.2% in forced expiratory volume in one second (FEV₁, one RCT, n=40 patients) and a reduction in mean partial pressure of CO₂ (one case study, n=7 patients), but there was no significant difference between furosemide and salbutamol (two RCTs, n=104 patients) or between furosemide and saline (one RCT, n=42 patients). Nebulized furosemide showed a protective action against the following bronchoconstrictive agents in experimentally induced asthma; adenosine 5'-monophosphate (p<0.01 and p<0.05; two RCTs n=20 participants), ultrasonically nebulized distilled water (p<0.01 to p<0.001; three RCTs, n=38 participants), sodium metabisulphite (p<0.05 to p<0.001; one RCT, four RCCTs, n=59 participants) and aspirin (no p-values reported; two RCCTs, n=22 participants). Furosemide also showed a protective
action against exercise induced asthma (p<0.01; three RCTs and one RCCT, n=44 participants), allergen induced asthma (p<0.05; one RCT and one RCCT, n=21 participants), dry air (p<0.01; one RCCT, n=15 participants), and isocapnic hyperventilation (p<0.04 to p<0.002; three RCTs, n=30 participants). Results for the protective action of furosemide against methacholine were mixed.

**Cancer**: One open clinical trial of patients with cancer (n=15 patients) found significant reductions in sense of effort (p=0.013) and anxiety (p=0.04) with nebulized furosemide, but no significant differences in physiological measures. One case study of three cancer patients found that nebulized furosemide provided effective relief from dyspnoea where standard treatments had failed.

**Chronic obstructive pulmonary disease (COPD)**: One RCCT (n=19 patients) found that nebulized furosemide significantly improved FEV\(_1\) (p=0.038) and subjective perception of dyspnoea (p=0.0140) in patients with COPD.

**Healthy subjects**: In healthy adults, nebulized furosemide protected against: cough induced by prostaglandin F2-alpha (p<0.005; one RCCT, n=8 participants); methacholine induced bronchoconstriction (no p values reported; one RCT, n=22 participants); breath holding and resistive flow loading and hypercapnia-induced bronchoconstriction (p<0.05; one RCCT, n=12 participants). Four studies reported a small incidence of increased diuresis with nebulized furosemide.

**Reported adverse events**: Ten studies reported no adverse events.

**Authors' conclusions**
Nebulized furosemide appeared to have a positive effect on dyspnoea and physiological measurements, but the conclusions were limited by the small scale or methodological limitations of the many included studies.

**CRD commentary**
The review addressed a clear question with well-defined inclusion criteria for intervention. However, the inclusion criteria were broad for study design, participants and outcomes. Three relevant databases were searched. However, the articles were limited to English and there did not appear to have been a systematic search for unpublished data, so the possibility of language and publication bias cannot be ruled out. It was unclear whether the authors took the necessary steps to minimise the possibility of reviewer error and bias in the review process. Furthermore, a validity assessment did not appear to have been carried out, so it was not possible to determine the methodological quality of the included studies. Given the clinical heterogeneity between studies, the decision to combine the results in a narrative synthesis was appropriate. Given the unclear quality of the included studies and the possibility of error or bias in the review process, the reliability of the authors' conclusions is unclear and their caution is justified.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that further studies are needed on the safety, efficacy and indications for nebulized furosemide.

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