Reviewer's report

Title: Is nebulized saline a placebo in COPD?

Version: 2 Date: 15 July 2004

Reviewer: PN Black

Reviewer's report:

General

In the United Kingdom (and in a number of other countries) it is not unusual for patients admitted to hospital with exacerbations of COPD to receive “as required” nebulised saline in addition to regular nebulised bronchodilators. Although many clinicians are convinced of the value of this intervention, others remain sceptical. One of the common criticisms is that nebulised saline is just a placebo. To some extent this criticism is academic. If there is a cheap, safe and effective treatment that relieves a distressing symptom it doesn’t really matter how it works. Nonetheless if it could be shown that the use of nebulised saline is not just a placebo treatment it may lead to wider acceptance of this as a treatment for patients admitted to hospital with exacerbations of COPD. Khan and O’Driscoll have addressed this question in their study. They used an ingenious approach to address this problem. An ineffective nebuliser that produces large particles that will be deposited in the pharynx was compared with an Acorn nebuliser that produces smaller particles that are more likely to be deposited in the airways. Only the Acorn nebuliser led to a reduction in breathlessness. The difference between the two treatments was not only statistically significant but was also clinically relevant. This study suggests that effects of nebulised saline are not just due to a placebo effect. It also provides evidence that the effects are mediated through deposition of the saline aerosol in the airways as opposed to effects on the face or pharynx. In a previous study we found that nebulised saline delivered from a face mask reduces breathlessness (Poole PJ et al). We had speculated that this was due to the cooling effect of a wet aerosol on the face but more recently we found that this effect was not reduced when a local anaesthetic was applied to the face. In light of the study by Khan and O’Driscoll our observations are not surprising. The authors suggest that saline relieves breathlessness by improving sputum clearance. Although nebulised saline can promote sputum clearance this may just be coincidence. I think the authors should be a little more tentative when they make this suggestion. Perhaps it would be better to suggest that “The results of the present study are possibly explained by airway-moistening and sputum-inducing effects of nebulised saline” (Pg10, paragraph 1).

A study such as this always invites the criticism that it was not double-blind. In reality there is no way that this study could be double-blind because of the use of two different types of nebuliser and I think that a single blind design is acceptable. Ideally the randomisation should have been performed by an independent party and not the investigators and it would have been preferable if the study had been used a strictly parallel design. However I think these are minor criticisms rather than major criticisms and I doubt that the results would have differed if a more rigorous approach to randomisation had been used.

In a disease such as COPD where the airflow obstruction is largely irreversible the focus of treatment should be on ameliorating symptoms. This is an interesting study that addresses this issue. It provides further evidence that nebulised saline can relieve breathlessness and provides new insights into the way that this might work.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

The authors suggest that saline relieves breathlessness by improving sputum clearance. Although nebulised saline can promote sputum clearance this may just be coincidence. I think the authors should be a little more tentative when they make this suggestion. Perhaps it would be better to suggest that “The results of the present study are possibly explained by airway-moistening and sputum-inducing effects of nebulised saline” (Pg10, paragraph 1).

In the discussion (Pg 11 paragraph 2) the authors say that “The small (4%) improvement in breathlessness in the placebo group was probably a genuine placebo response”. This effect is not only small, it is not statistically significant and it is equally consistent with no effect at all. I think this sentence should be omitted.

In Table 2 the results are shown both as medians and means. If the data is not normally distributed it would seem more sensible to omit the mean values and just show the medians. This would also make the table less cluttered and easier to read. With Table 2 it would also be clearer if the Subjective Score was called the “Breathlessness Score”. Consideration should also be given to showing the symptom relief score separately on a third table. This would again make the results easier to read.

The references need to be checked more carefully. I can identify a few errors and there may be others. In Reference 2 there is no initial for the third author (Douglass). In Reference 8 the first author should be Sutherland ER. In reference 11 “chronic” is misspelt.

On page 5 the brackets for (reference) 12 are missing.

The authors alternate between using nebulized and nebulised. A consistent spelling should be used.

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Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

None