A Meta-analysis of the Effects of Ipratropium Bromide in Adults with Acute Asthma
Rodrigo G, Rodrigo C, Burschtin O
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Is the question clearly focused?

Yes

What is being reviewed?

Does adding an anticholinergic agent to beta-agonists provide added benefits for adults with acute asthma in the early stages of the disease?

What is the population?

Adults (over 16y) with acute asthma or status asthmaticus treated in A&E with beta-agonists.

What is the exposure/intervention?

Ipratropium bromide

What is the outcome?

Main outcome is pulmonary function, secondary outcome is hospital admission rate.

Is the search thorough?

Yes, but not as thorough as it might have been. They did state their search terms.

Bibliographic database; years covered?

Medline 1978 – April 1999. (One wonders then how they managed to submit the manuscript in 1998 – maybe they updated it when they revised the manuscript, submitting again in May possibly and getting accepted in June)

Current contents, Science Citation Index, review articles – no information given about years covered.

Not EMBASE – this is an important database that will often have a significant number of studies not indexed in Medline

References in relevant articles?

References of identified articles, but not references of references

Grey literature (unpublished research reports etc)?

Medical Editor's Trial Amnesty
Pulmonologists and emergency physicians
Manufacturer of drug

Not conference abstracts

Are the inclusion criteria appropriate?

Adults > 16y – yes
English language – no
Randomised, double-blind, controlled clinical trials which addressed :
- Acute exacerbation of asthma - Yes
- Treatment in an emergency department with beta agonists - Yes

Is the validity of included studies adequately assessed?

Is assessment reproducible, blind?

Two reviewers looked at the selected papers independently with authors and outcomes blinded. Differences were resolved by consensus and the two rated their agreement using a Kappa statistic – agreement was rated as very good.

Kappa is used to assess agreement for two assessments of a categorical variable. For example, if two people each assess ten people as to eye colour they may agree, because they get it right, or they may agree by chance, or they may disagree because they get it wrong, or they may get it wrong by chance. The measure looks at what proportion are right that is above that you would get by chance alone.

Is missing information obtained from investigators?

They don't mention it. Their primary outcome seemed to have been assessed in all studies they collected – perhaps they were lucky, or did they have that as an inclusion criterion? Their secondary outcome was used if it was reported but no attempt was made to gather that information from authors if it was absent.

Is publication bias an issue?

They have used a funnel plot (fig 3) to visualize this and have done a calculation to see if a line of best fit drawn through the points is significantly away from the vertical. The funnel plot shows a complete absence of negative trials amongst the small studies. The authors discuss this and remark that, by not including non-English studies and by not searching EMBASE, (and also by not considering abstracts) there is a reason why negative studies could be missing be cause of publication bias. Based on the statistics, however, they say that the plot was symmetrical (intercept 0.34, 90% CI –0.71 to 1.39. Also what they say is not correct – a non statistical result cannot prove that the plot is symmetrical, only that they cannot say that it is not. Given the paucity of results in the funnel plot, and the wide confidence interval, it seems likely that there is not sufficient power using this particular method to detect a lack of symmetry.

Has methodological quality been assessed?

Quality score was used but their method did not include any scoring for allocation concealment and intention to treat analysis in the original study – both of these are potential large sources of bias. The quality score has not been used as an inclusion criteria, only to look for potential bias, which they saw, although it was not significant "there were weak correlations …..between effect size and methodological quality …".

How big is the overall effect?

Not very big for an improvement in pulmonary function, but large for hospital admission rates.

On what scale is the effect measured?

The main outcome is assessed using the effect size measured in relation to standard deviation units. The effect size was only 0.14. Remembering that 95% of all possible observations, if there is no difference between the treatments, will lie within the middle (0), +/- about 2 sd, then an sd of 0.14 is not very impressive and they stated that anything less than 0.2 they would also call small.

They have used odds ratios for hospital admission. The overall odds ratio is 0.62. This means that the admission rates on the new treatment is 62% of the control, or 38% less than the control.

(Odds ratios can be interpreted in several ways.

For example an odds ratio of 1.6 means that the odds in the treatment group is 1.6 times that in the control group, or is 60% more in the treatment group.

An odds ratio of 2.0 means that the odds in the treatment group is 2 times that in the control group, or is 100% more in the treatment group.

An odds ratio of 10.0 means that the odds in the treatment group is 10 times than in the control group, or 900% more in the treatment group.

An odds ratio of 0.6 means that the odds in the treatment group is 0.6 times that in the control group or 40% less in the treatment group.)

Are the results consistent between studies?

Yes – all points of the effect size for the studies lie on the side that favours ipratropium bromide. They also undertook a test for homogeneity which was not significant. This test checks for consistency between studies, with things like smaller studies having wider confidence intervals, and larger studies tending to show similar point effect sizes.

The text is slightly confusing since this might be interpreted as meaning that the test was saying that there was not significant homogeneity – in other words suggesting that the sample was heterogeneous. The following words clarify that they intend the reverse (indicating similar treatment effects) – that the test is to detect a lack of homogeneity, and that it was not significant.

How sensitive are the results to changes in the way the review is done?

They undertook a sensitivity analysis, leaving out low quality studies which also showed the largest point effect, and also considered trial size, severity of patients, and whether or not the patients were on steroids at the start of the study. They also showed that it would take about 37 other small studies, not so far considered, that showed that the treatments were not different in order to change the overall effect size to be non-significant, and this is despite the effect being very small. This might seem rather a lot but they have only assumed small negative studies since these are the very ones that are less likely to have been published.

How precise are the results?
Does the lower confidence limit include clinically relevant effects? OR
Does the upper confidence limit exclude clinically relevant effects?

The lower end of the confidence interval for the pooled effect is 0.04sd. Because it does not extend the other side of 0 it is said to be statistically significant but this level translates into about a 2% difference, probably not clinically useful. The upper end is 0.24sd, an 18% difference, which, if this were true, would be very useful.

Do conclusions flow from the evidence reviewed?

Yes – a small benefit in pulmonary function – a substantial difference in hospital admission. In considering pulmonary function the confidence interval puts us in doubt about whether we can be convinced of the clinical benefit – in such situations one could consider other things which would help in the decision making process, such as cost. Clearly the effect on admission rates would be very persuasive.

Are subgroup analysis interpreted cautiously?

Those studies with patients showing extreme obstruction on average, showed greater benefit with ipratropium bromide. Although mentioned in the abstract this information does not form

part of the summary paragraph. Studies which detailed hospital admission rates showed substantial benefit with this drug. Although only 5 studies were included they composed 80% of the patients.

Can the conclusions and data be generalised to other settings?

Probably. Other meta-analyses involving children have found similar results. Table 2 gives the age ranges of people in the study – 95% are less than about 60 years old. Probably mainly caucasian.

(Age is 32+/-13sd – 95% reference range is 32+/-2x13 = up to 58y – i.e. about 60y)

Is NNT (numbers needed to treat) stated or able to be calculated?

Not stated. Can't calculate as the measure of effect size is not given in absolute terms but relative to the pooled standard deviation.

Are recommendations linked to the strength of the evidence?

Yes Given that only short term effects (90 mins) are considered and that response may be increased with more bronchdilators, they have suggested looking specifically at the latter.