

Indirect comparisons of competing interventions

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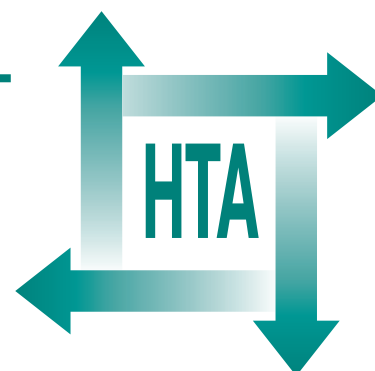
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Executive summary

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Executive summary

Background

The randomised controlled trial (RCT) is the most valid design for evaluating the relative efficacy of healthcare technology. However, many competing interventions have not been directly compared in RCTs and indirect methods have been commonly used in meta-analyses. Such indirect comparisons are subject to greater bias (especially selection bias) than head-to-head randomised comparisons, as the benefit of randomisation does not hold across trials. Therefore, it is essential to evaluate such bias that may lead to inaccuracies in the estimates of treatment effects and result in inappropriate policy decisions.

Objectives

The objectives of this study were:

- to survey the frequency of use of indirect comparisons in systematic reviews and evaluate the methods used in their analysis and interpretation
- to identify alternative statistical approaches for the analysis of indirect comparisons
- to assess the properties of different statistical methods used for performing indirect comparisons
- to carry out empirical work comparing direct and indirect estimates of the same effects within reviews.

Methods

The Database of Abstracts of Reviews of Effects (DARE) (1994 to March 1999) was searched for systematic reviews involving meta-analysis of RCTs that reported both direct and indirect comparisons, or indirect comparisons alone. A systematic review of MEDLINE (1966 to February 2001) and other databases was carried out to identify published methods for analysing indirect comparisons.

Study designs were created using data from the International Stroke Trial. Random samples of patients receiving aspirin, heparin or placebo in 16 centres were used to create meta-analyses, with

half of the trials comparing aspirin and placebo and half heparin and placebo. Methods for indirect comparisons were used to estimate the contrast between aspirin and heparin. The whole process was repeated 1000 times and the results were compared with direct comparisons and also theoretical results.

Further detailed case studies comparing the results from both direct and indirect comparisons of the same effects were undertaken.

Results

Of the reviews identified through DARE that included meta-analyses of two or more RCTs, 31/327 (9.5%) included indirect comparisons. A further five reviews including indirect comparisons were identified through electronic searching. Few reviews carried out a formal analysis. Some reviews based analysis on the naive addition of data from the treatment arms of interest. Interpretation of indirect comparisons was not always appropriate.

Few methodological papers were identified. Some valid approaches for aggregate data that could be applied using standard software were found: the adjusted indirect comparison, meta-regression and, for binary data only, multiple logistic regression (fixed effect models only).

Simulation studies showed that the naive method is liable to bias and also produces over-precise answers. Several methods provide correct answers if strong but unverifiable assumptions are fulfilled. Four times as many similarly sized trials are needed for the indirect approach to have the same power as directly randomised comparisons.

Detailed case studies comparing direct and indirect comparisons of the same effect show considerable statistical discrepancies, but the direction of such discrepancy is unpredictable.

Conclusions

When conducting systematic reviews to evaluate the effectiveness of interventions, direct evidence

from good-quality RCTs should be used wherever possible. If little or no such evidence exists, it may be necessary to look for indirect comparisons from RCTs. The reviewer needs, however, to be aware that the results may be susceptible to bias.

When making indirect comparisons within a systematic review, an adjusted indirect comparison method should ideally be used using the random effects model. If both direct and indirect comparisons are possible within a review, it is recommended that these be done separately before considering whether to pool data.

Recommendations for research

There is a need for evaluation of methods for analysis of indirect comparisons for continuous data.

There is a need for empirical research into how different methods of indirect comparison perform in cases where there is a large treatment effect.

Further research is required to consider how to determine when it is appropriate to look at

indirect comparisons and how to judge when to combine both direct and indirect comparisons. Research into how evidence from indirect comparisons compares to that from non-randomised studies may also be warranted.

Empirical investigations were based on one large, multicentre trial with a common protocol across each centre. It would be useful to repeat the investigations using individual patient data from a meta-analysis of several RCTs using different protocols.

The odds ratio was used as the measure of effect within this simulation study. Although logistic regression calls for the effect measure to be the odds ratio, it would be interesting to evaluate the impact of choosing different binary effect measures for the inverse variance method.

Publication

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NHS R&D HTA Programme

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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