Title	**Indirect Comparisons of Competing Interventions**
Agency	**NCCHTA, National Coordinating Centre for Health Technology Assessment**
	Mailpoint 728, Boldrewood, University of Southampton, Southampton SO16 7PX, United Kingdom; Tel: +44 2380 595586, Fax: +44 2380 595639
Reference	Health Technol Assess 2005;9(26). July 2005. www.ncchta.org/execsumm/summ926.htm

Aim

- To survey the frequency of using indirect comparisons in systematic reviews and evaluate the methods used in analysis and interpretation.

- To identify alternative statistical approaches in analyzing indirect comparisons.

- To assess the properties of different statistical methods used to perform indirect comparisons.

- To compare direct and indirect estimates of the same effects in reviews.

Conclusions and results

Of the reviews found in DARE, 31/327 (9.5%) included indirect comparisons. Electronic searching yielded another 5 reviews including indirect comparisons. Few reviews carried out a formal analysis, and some based analysis on the naive addition of data from treatment arms. Few methodological papers were identified. Some valid approaches for aggregate data that involved standard software were found (adjusted indirect comparison, meta-regression, multiple logistic regression). Simulation studies showed that the naive method is liable to bias and also produces over-precise answers. Several methods yield correct answers if strong but unverifiable assumptions are met. Four times as many similarly sized trials are needed for the indirect approach to have the same power as directly randomized comparisons. Detailed case studies comparing direct and indirect comparisons of the same effect show considerable statistical discrepancies, the direction of which is unpredictable.

Recommendations

Systematic reviews to evaluate the effectiveness of interventions should use direct evidence from good-quality RCTs. If little or no such evidence exists, it may be necessary to look for indirect comparisons from RCTs. The reviewer should be aware that the results might be susceptible to bias. When making indirect comparisons in a systematic review, an adjusted indirect comparison method involving the random effects model should be used. If both direct and indirect comparisons are possible in a review, these should be done separately before considering whether to pool data.

Methods

The Database of Abstracts of Reviews of Effects (DARE) was searched for systematic reviews involving meta-analysis of randomized controlled trials (RCTs) that reported on direct and indirect comparisons, or indirect comparisons alone. A systematic review of MEDLINE and other databases was carried out to identify published methods for analyzing indirect comparisons. Study designs were created using data from the International Stroke Trial. Random samples of patients receiving aspirin, heparin, or placebo in 16 centers 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 process was repeated 1000 times, and results were compared with direct comparisons and theoretical results. Detailed case studies were undertaken to compare the results of direct and indirect comparisons of the same effects.

Further research/reviews required

- Evaluate methods for analysis of indirect comparisons for continuous data

- Empirical research into how different methods of indirect comparison perform in cases where the treatment effect is large

- Determine when it is appropriate to look at indirect comparisons and how to judge when to combine both direct and indirect comparisons

- Compare evidence from indirect comparisons and nonrandomized studies

- Repeat the empirical investigations using individual patient data from a meta-analysis of several RCTs using different protocols

- Evaluate the impact of choosing different binary effect measures for the inverse variance method.

Written by Ms Alison Eastwood, CRD, University of York, United Kingdom