International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 2(1): January-February 2012

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Medical Sciences **Brief Report……!!!**

Received: 17-01-2012; Accepted: 25-01-2012

INTRICACIES OF META-ANALYSIS

Dr. Barkha Bindu

Junior Resident, Department of Anaesthesia, Gandhi Hospital, Mushreeabad, Secundrabad, Hyderabad, Andhra Pradesh, India

Keywords:

Meta-Analysis**,** randomized, systematic

For Correspondence:

Dr. Barkha Bindu

Junior Resident, Department of Anaesthesia, Gandhi Hospital, Mushreeabad, Secundrabad, Hyderabad, Andhra Pradesh, India

E-mail:

barkha_bindu@yahoo.co.in

ABSTRACT

Inconsistency of studies' results in a meta-analysis reduces the confidence of recommendations about treatment. An individual patient's data based meta-analysis leads to optimal data quality and allows more extensive analyses, generating more hypotheses for further trials. In spite of advances in meta-analytic method that are meant to increase the precision of literature review, meta-analysis is still, in many ways, a very human enterprise.

INTRODUCTION

Meta-analysis term was coined by Glass[1] in 1976 to describe an approach to quantitatively reviewing a research literature. According to Khan et al[2]. 2003 "Meta-analysis is a statistical technique for combining the individual effects of a number of studies addressing the same question to produce a summary effect". Results of large trials, i.e. trials including more than 1000 patients, and of meta-analyses have been compared in several publications. Issues have been raised about the usefulness of meta-analysis. LeLorier et al. for instance failed to predict correctly the results of large trials investigating the same question as reported by several meta analyses of small trials[3] while Cappelleri et al. able to do so[4]. He also provided some explanations in case of differences. Well conducted meta-analyses and large trials are not competing research tools, they are complementary to each other.

The first set of Cochrane reviews dealt with studies in neonatology, and one especially creative critic, cited by Mann (1990)[5], called the reviewers an obstetrical

Baader Meinhof gang (obstetrical being a reference to the field of research, and Baader Meinhof gang a reference to the terrorist group that operated in Europe during the 1970s and 1980s). Others were more vague in their comments. Eysenck(1978)[6] criticized as an exercise in mega-silliness. Shapiro (1994) [7] published a paper entitled Meta-Analysis / Shmeta Analysis. Feinstein (1995)[8] in his editorial referred meta-analysis as 'statistical alchemy for the 21st century'. For their creative use of met-analysis some of these criticisms are worth mentioning.

Summary effect

The treatment effect may vary from study to study but meta-analysis results mainly focuses on the summary effect but ignores other fact. For combining studies and for concluding consistency or inconsistency of findings tests for heterogeneity are commonly used to decide on methods[910]. Bailar (1997)[11,12] for example, writes, 'Any attempt to reduce results to a single value, with confidence bounds, is likely to lead to conclusions that are wrong, perhaps seriously so'. Meta-analyses often include small numbers of studies[10,13] and the power of the test in such circumstances is low[14,15]. For example, consider the meta-analysis of randomised controlled trials of amantadine for preventing influenza.[16] The treatment effects in the eight trials seem inconsistent: the reduction in odds vary from 16% to 93%, with some of the confidence intervals not overlapping. But the test of heterogeneity yields a P value of 0.09, conventionally interpreted as being non-significant. Because the test is poor at detecting true heterogeneity, a non-significant result cannot be taken as evidence of homogeneity. Using a cut-off of 10% for significance ameliorates this problem but increases the risk of drawing a false positive conclusion (type I error).[15] one who ignore heterogeneity and report a summary effect are indeed missing the point of the synthesis.

Bias in selecting the studies

Publication bias is a potential threat in all areas of research including quantitative reviews and meta-analysis. Several evidence show that studies with relatively high treatment effects are more likely to be published than studies finding negative finding. The later unpublished, research lies dormant in the researchers' filing cabinets, and has led to the use of the term file drawer problem for meta-analysis. If former studies are biased then mean effect will reflect the bias. Therefore publication bias is a problem also who searches the database. Yusuf et al.[18] for the first time included unpublished data, it leads to a more adequate analysis of results at a minimal cost, however, quality control and data analyses are limited.

Mixing of Apples and oranges

The studies that are included in meta-analysis will differ in their characteristics, measured different things, manipulated different variables, and tested different subject populations. Glass defended this mixing by analogy to how "apples and oranges" can be subsumed under the superordinate category of "fruit" (Smith et al., 1980).[19]

The main aim of meta-analysis is to answer the broader question rather than individual studies. The decision as to which studies should be included or excluded is always a judgment. Some meta-analysts may make questionable judgments while other may make unreasonable demands on similarity. Example that a treatment is very effective for patients in increasing progression free survival but no effect on disease free or overall survival. If we were to combine data from studies that used both types of patients, and conclude that the treatment was modestly effective (on average), this conclusion would not be accurate for either kind of patient. If we were to restrict our attention to studies in only group of patients. we could report how the treatment worked with one type of patient, but could only speculate about how it would have worked with the other type. By contrast, a meta-analysis that includes data for both types of patients may allow us to address this question empirically. Turner et al[20] analyzed the publication status of studies of antidepressants. Based on studies registered with the US Food and Drug Administration (FDA), they found that 97% of the positive studies were published vs only 12% of the negative ones. Furthermore, when the nonpublished studies were not included in the analysis, the positive effects of individual drugs increased between 11% and 69%.

Garbage In, Garbage Out

Eysenck et al. 1978 concerns the quality of the primary research included in reviews Good and poor studies may not differ in mean effect size, but in distribution. A meta-analysis will always have a set of inclusion criteria and these should include criteria based on the quality of the study. If a meta-analysis includes many low-quality studies, then fundamental errors in the primary studies will be carried over to the meta-analysis, where the errors may be diffcult to identify. Suppose that ten studies used an acceptable method to randomize patients while another ten used a questionable method. In the analysis we can compare the effect size in these two

subgroups, and determine whether or not the effect size actually differs between the two. Note that such analyses (those comparing effects in different subgroups) can have very low power so need to be interpreted carefully, especially when there are not many studies within subgroups. Importantly, in meta-analysis the criteria are transparent and are described as part of the report. Studies should be sufficiently similar to yield results that can be interpreted, and sufficiently free of bias to yield results that can be believed.

META-ANALYSES ARE PERFORMED POORLY

John C. Bailar[11,12], in an editorial for the New England Journal of Medicine (Bailar, 1997), writes that mistakes such as those outlined in the prior criticisms are common in meta-analysis. He argues that a meta-analysis is inherently so complicated that mistakes by the persons performing the analysis are all but inevitable. He also argues that journal editors are unlikely to uncover all of these mistakes.

META-ANALYSIS CAN DISAGREE WITH RANDOMIZED TRIALS

Metaanalyses can sometimes yield different results than large scale randomized trials. LeLorier et al. (1997)[3] stated that result of meta-analysis disagree with randomized control studies in 34%. Since randomized control studies are gold standard so the author concluded that 34% of meta-analysis are wrong and cannot be trusted. Consider the following scenario. Radiotherapy is introduced, to increase the survival in low grade glioma. Radiotherapy is tested in a randomized trial involving patients with a very poor prognosis, and yields a risk ratio of 0.55. Based on these encouraging results, it is tested in patients with a somewhat better prognosis. Since the patients in this group are more likely to survive longer, the impact of radiotherapy is less pronounced, and the risk ratio is 0.61. If radiotherapy is being tested with all patients, and the risk ratio is 0.82. These are the studies included in the meta-analysis. The new trial is performed using a relatively healthy population and (following the trend seen in the meta-analysis) yields a risk ratio of 0.91. If one were to report a mean effect of 0.67 for the meta-analysis versus 0.91 for the new trial there would indeed be a problem. But the meta-analysis should focus on the dispersion in effects and try to identify the reason for the dispersion. In this example, using either extent of surgical resection or study year as a covariate we can explain the pattern of the effects, and would have predicted that the effect size in the new study would fall where it did.

LeLorier et al[3] compared the results of 19 meta-analyses and 12 large randomized controlled trials on similar topics. In 5 (12%) out of 40 trials were significantly different than those of the meta-analysis. Publication bias, study heterogeneity, and differences in populations were plausible explanations for the disagreements. However, author correctly commented: “this does not appear to be a large percentage, since a divergence in 5 percent of cases would be expected on the basis of chance alone.”

CONCLUDING REMARKS

Inconsistency of studies' results in a meta-analysis reduces the confidence of recommendations about treatment. Criticisms raised in this is to problems with meta-analysis. We have argued that these problems exist also for the narrative review, and that the key advantage of the systematic approach of a meta-analysis is that all steps are clearly described so that the process is transparent. An individual patient's data based meta-analysis leads to optimal data quality and allows more extensive analyses, generating more hypotheses for further trials. In spite of advances in meta-analytic method that are meant to increase the precision of literature review, meta-analysis is still, in many ways, a very human enterprise.

REFERENCES

1. Glass, G. V. Primary, secondary, and meta-analysis of research. Educational Researcher1976;5:3-8.
2. Bailar JC 3rd. The Promise and Problems of Meta-Analysis. N Engl J Med 1997;337:559-61.
3. LeLorier J, Grégoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. N Engl J Med 1997;337:536-42.
4. Ioannidis JP, Cappelleri JC, Lau J. Meta-analyses and large randomized, controlled trials.N Engl J Med. 1998;338:59;author reply 61-2.
5. Mann C. Meta-analysis in the breech. Science 1990;249:476-80.
6. Eysenck H J. An exercise in mega-silliness. Am Psychol 1978;33:517.
7. Shapiro S. Meta-analysis/Shmeta-analysis. Am J Epidemiol 1994;140:771-8.
8. Feinstein AR. Meta-analysis: Statistical alchemy for the 21st century. J Clin Epidemiol 1995;48:71-9.
9. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al.The Cholesterol Treatment Trialists' (CTT). Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005 ;366:1267-78
10. Neal B, MacMahon S, The Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other bloodpressure- lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet 2000;9:1955–64.
11. Bailar JC III. The practice of meta-analysis. J Clin Epidemiol 1995;48:149-157.
12. Bailar, Promise and problems of meta-analysis. New Engl J Med 337: 559–561.
13. Pignon JP, Hill C. Meta-analysis of randomised clinical trials in oncology. Lancet Oncol 2001;2:475–82.
14. Yusuf S, Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;27:335–71.

15. Egger M, Davey Smith G. Misleading meta-analysis. Lessons from "an effective, safe, simple" intervention that wasn't. BMJ 1995;310:752-4.
16. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic orimmunetherapy: 133 randomised trials involving 31,000 recurrences and 24,000 death among 75,000 women. Lancet 1992;339:1–15, 71–85.
17. Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, et al. A meta-analysis of thoracic radiotherapy for small cell lung cancer. New Engl J Med 1992;327:1618–24.
18. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;27:335–71.
19. Smith, Publication bias and meta-analysis.Evaluation in Education.1980;4: 22-4.
20. Turner EH, Matthews AM, Linardatos E, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008; 358:252–260.