SYSTEMATIC REVIEWS AS A TOOL FOR PLANNING AND INTERPRETING TRIALS

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Abstract

Background: Systematic reviews followed by a meta analysis are carried out in medical research to combine the results of two or more related studies. Stroke trials have struggled to show beneficial effects and meta-analysis should be used more widely throughout the research process to either speed up the development of useful interventions, or halt more quickly research with hazardous or ineffective interventions.

Summary of review:This review summarises the clinical research process and illustrates how and when systematic reviews may be used throughout the development programme. Meta-analyses should be performed after observational studies, preclinical studies in experimental stroke, and after phase I, II and III clinical trials and phase IV clinical surveillance studies. Although meta-analyses most commonly work with summary dichotomous data, they may be performed to assess relationships between variables (meta-regression) and, ideally, should utilise individual patient data. Meta-analysis techniques may also work with ordered categorical outcome data (ordinal meta-analysis) and be used to perform indirect comparisons where original trial data do not exist.

Conclusion:Systematic review/meta-analyses are powerful tools in medical research and should be used throughout the development of all stroke and other interventions.

Keywords: Stroke, meta analysis, clinical trials, epidemiology

Introduction

Trials in acute stroke have struggled to identify effective interventions, the few successes including alteplase, aspirin, hemicraniectomy, and stroke units.[1-5] In contrast, numerous interventions have been ineffective or even hazardous, including neuroprotectants and anticoagulants.[6,7] Although there are many reasons to explain these failures, a central one is that most research programmes developing a new intervention do not analyse the results from their latest study in the context of existing data for that treatment. As a result, programmes often progress further than their existing data warrant. The techniques of systematic review and meta-analysis (quantitative systematic review) allow integration of data from separate but related sources. Meta-analyses may encompass data from observational studies, pre-clinical animal studies, or clinical human trials and should be integrated into the development plan of any new intervention (figure 1).

Definition

A systematic review is: '*A summary of the medical literature that uses explicit methods to perform a thorough literature search and critical appraisal of individual studies and that uses appropriate statistical techniques to combine these valid studies*' (www.jr2.ox.ac.uk/bandolier/booth/diagnos/glossary.html).

Doing a systematic review

A standard sequence of events is necessary in performing a systematic review. The review needs a precise question; definition of which trials are to be included and excluded, and how these will be identified; what outcomes are to be collected; how numerical data will be integrated and analysed; and how the results will be interpreted.

These decisions should be laid out in a protocol prior to performing the review itself, not least to prevent data-driven analyses and interpretations of the results.

Systematic reviewing and meta-analysis are no different from any other scientific technique in that there are advantages and disadvantages, and strengths and weaknesses, in the process. So inadequate definition of the protocol, poor searching of suitable studies, publication bias (whereby neutral or negative trials remain unpublished and therefore cannot be found), poor trial quality, data driven analyses, selective reporting of outcomes, and biased interpretation of the results, can each damage the value of the review and even change its conclusions.

Observational studies

The basis for some candidate interventions can be derived from the results of observational studies. The results from such studies may be integrated using systematic review techniques to provide a summary estimate. For example, several small studies have reported that a high blood pressure during the acute phase of stroke is associated with a poor outcome; a meta-analysis subsequently confirmed this finding [8] and provides justification for studying the effect of lowering blood pressure, as several trials are now doing.

Preclinical studies

The development programme for most interventions starts with preclinical studies in experimental models of stroke followed by clinical studies. The decision to move from laboratory to the clinic is often made on the basis of a few positive animal studies without considering all the available experimental data (whether published or

unpublished), some of which may be neutral or negative. A quantitative systematic review (including meta-analysis) of preclinical data should be performed prior to any decision to start clinical studies.[9] The review should address explicitly the STAIR I criteria [10] for experimental data, these including the effect of the intervention by dose, timing of administration, stroke model (transient, permanent), species (ideally including a primate), age and sex of animal, and presence of co-morbidities (hypertension, hyperlipidaemia, diabetes). Unfortunately, preclinical studies have not always antedated clinical trials. In one case, review of preclinical studies found that nimodipine was only mildly neuroprotective,[11] this information becoming available after clinical studies had largely finished; unsurprisingly, a meta-analysis of the clinical trials was neutral.[12] Such systematic reviews of preclinical work are useful for justifying the funding, whether commercial of academic, of clinical studies, as seen for nitric oxide in stroke [13] which underpins the ongoing MRC ENOS trial (www.enos.ac.uk/).[14] The CAMARADES (http://www.camarades.info/) collaboration is coordinating the development of systematic reviews in preclinical stroke. Such systematic reviews can also identify potential problems in the design and conduct of preclinical studies.[15]

Phase II clinical trials

Conventionally, several randomised phase II trials are done to investigate the safety, tolerability, and feasibility of administration of a new intervention, and to identify suitable doses and potential mechanisms of action, and signals of potential efficacy based on surrogate measures. A systematic review of the clinical use of the intervention should be initiated at the beginning of phase II, this being updated as each phase II trial is completed. Whilst individual phase II trials are grossly underpowered to assess efficacy, systematic reviews based on several trials may show trends helpful for making further

decisions on stopping or continuing the development programme. In this respect, it is questionable whether phase III trials of gavestinel would have been done if the results of a systematic review of phase II trials [6] had been published prior to the decision to proceed to formal studies of efficacy, these ultimately being neutral.[16] In contrast, phase II trials of intravenous magnesium were promising [6] although the IMAGES phase III trial was unfortunately neutral.[17] Similarly, phase II trials of abciximab suggested potential benefit [18,19] although this was not realised in a subsequent phase III trial.[20] In these examples of magnesium and abciximab, although the phase III trials were ultimately neutral, the summary of phase II trials at least justified proceeding with further development.

Phase III clinical trials and end of development

Systematic reviews have two main roles once a phase III programme has been completed. Ideally, they will be used to sum up all the available data, as done with positive interventions such as aspirin (for acute ischaemic stroke [3]) and dipyridamole (for secondary prevention [21]) as well as neutral (e.g. lubeluzole [22]) and negative (e.g. selfotel [23]) interventions. Systematic reviews of positive phase III trials will help regulatory approval, and can support changes in guidelines and, ultimately, medical practice. In other cases, systematic reviews will identify a strong trend justifying further trials, as with citicoline in acute stroke,[24] or areas where further research is required with a proven intervention, e.g. potentially extending the time window for intravenous alteplase [1,2] from 3 to 4.5 or even 6 hours, as being studied respectively in the ongoing ECASS III and IST-3 trials.[25]

The system of time-limited patents means that some drugs are incompletely studied although the available evidence, when integrated in a systematic review, suggests that further development might be warranted; there are several examples, one being pentoxifylline and related methylxanthine derivatives.[26] Finally, it may become clear that development of a particular intervention could potentially have been curtailed earlier than happened; for example, the meta-analysis may suggest a neutral effect whilst other trials are underway, as seen with low molecular weight heparins.[27,28] Worse, a signal of hazard may be present in the meta-analysis at a time when further trials are being designed (and subsequently take place), as occurred for tirilazad mesylate.[29] These examples provide strong justification for performing cumulative meta-analyses which need to be updated after each and every phase II and III trial; figure 2 shows the cumulative meta-analysis for tirilazad.

Phase IV studies

The introduction of a new intervention into clinical practice may not be the end of research studies, particularly if the treatment is controversial, perhaps because of significant side effects. So-called phase IV post-marketing studies may be performed to assess safety and efficacy in the real world, and these may be integrated systematically. For example, although alteplase was shown to improve functional outcome in hyperacute ischaemic stroke and was subsequently licensed, concerns about routine use by inexperienced staff and the potential for causing fatal intracerebral haemorrhage meant that a number of phase IV studies were done. These were integrated in a systematic review [30] which showed that safety was adversely affected if the protocol for administering alteplase was violated.

Individual patient data meta-analysis

Most of the quantitative systematic reviews quoted above used summary (or group) data from each trial. However, access to data at the subject rather than trial level allows individual patient data meta-analyses to be performed. Such analyses are considered to be the 'gold-standard' [31] since they allow effects to be studied in subgroups of patients; for example, the addition of dipyridamole to aspirin is more effective in preventing stroke recurrence than aspirin alone across several trials irrespective of age, qualifying event (stroke or TIA) and history of hypertension.[21] Additional subgroups may be calculated from the trial data, e.g. the effect of combined aspirin and dipyridamole relative to aspirin is constant across different baseline risk strata derived from the above baseline variables.[21] Unfortunately, if summary meta-analyses are complicated by missing trial data, this problem is magnified in analyses based on individual patient data, especially in older studies where databases have been discarded or are incompatible with modern computers and statistical software. If a prospective systematic review is to be updated during the development of a new intervention (as recommended above) then there is every reason to base this on individual patient data (rather than summary data) to facilitate subgroup analyses and meta-regression (see below).

An important example of a prospective individual patient meta-analysis is that describing the effect of early decompressive surgery for malignant infarction of the middle cerebral artery. Although surgery was known to reduce death, its effect on functional outcome was unclear and three trials were performed. The nature of the condition and intervention meant that any trial would be very small in size and its results unreliable; integration of the three data sets into a systematic review has confirmed the benefit of this intervention in carefully selected patients.[5]

Meta-regression

Summary data from trials are usually combined in one-dimension, that is by outcome. However, the relationship between outcome and potential modifying covariates can be assessed in two dimensions by plotting the variables in a scatter plot. These data may then be analysed using regression techniques to identify the mathematical relationship between the variables. A classic example in stroke is the curvilinear relationship between lowering blood pressure and stroke reduction in randomised controlled trials, these showing that greater blood pressure lowering leads to a larger reduction in subsequent stroke.[32] In the arena of preclinical stroke, the effect of nitric oxide synthase inhibitors in transient models of experimental ischaemia appears to decline as the time between the onset of ischaemia and starting treatment increases (figure 3).[33] Access to individual patient data facilitates meta-regression at the patient rather than trial level. As a result, the effect of one or more modulating variables on the relationship between the intervention and outcome can be studied in more detail. By example, the efficacy of thrombolysis falls as the stroke-needle time increases.[2]

Indirect comparisons

All of the analyses referred to above relied on direct comparative data. But, sometimes data comparing two interventions (e.g. 'A' versus 'B') may not be available although studies of each may have been performed against a third comparator (e.g. 'A' versus 'C', and 'B' versus 'C'). In this case, indirect comparisons of the agents may be performed using network or other indirect comparison meta-analysis techniques.[34] By example, the combination of aspirin and warfarin appears to be more effective than the combination of aspirin and clopidogrel in preventing thromboembolic stroke after acute coronary syndromes [35] while the combination of oestrogen and progesterone causes more venous

thromboembolic events (but not stroke) than oestrogen alone when used as hormone replacement therapy (Sare, Gray & Bath, unpublished).

Other uses of systematic review techniques

Systematic review techniques may be used for more than just analysing the potential efficacy of interventions. For example, the failure of many trials and interventions in acute stroke raises the possibility that there may be better approaches to analysing trial data than currently used. The 'Optimising Analysis of Stroke Trials' (OAST) Collaboration has confirmed standard statistical lore, using individual patient data from stroke trials, that ordinal analyses of ordered categorical data (as exists in the modified Rankin Scale) are more efficient than those based on dichotomous data.[36] Designing trials to use ordinal analyses (such as ordinal logistic regression) results in a 25-30% reduction in sample size although this advantage appears to depend on the type of intervention being studied (OAST Collaboration, unpublished data).

In an extension to this concept, it is possible to generate ordered categorical outcomes for vascular prevention trials. For example, the binary outcome of 'stroke/no stroke' may be converted into the 5 levels of outcome, e.g. 'fatal stroke/severe stroke/mild stroke/TIA/no event'. Using published outcome data from 80+ prevention trials, analysis of this ordinal data increased statistical power (or reduced sample size for a given power) as well as providing information on the effect of the interventions on stroke severity.[37] Importantly, ordered categorical data from trials may be meta-analysed in similar ways to binary data.[38]

Conclusion

The technique of systematic review, encompassing the numerical approach of meta-analysis, is a powerful ally in the development of new stroke interventions. It can be used to combine results from related studies, whether from epidemiology, pre-clinical animal studies, phase II explanatory trials, phase III efficacy trials, or phase IV post-marketing studies. It can also be used to help improve techniques for analysing and designing trials. Like any technique, systematic reviews have strengths and weaknesses, and the results may be misleading if the review is performed badly. Additionally, meta-analyses may obtain the wrong answer even if performed well, but this is true of all scientific techniques. Systematic reviews are not a surrogate for performing adequate numbers of adequate-sized trials, but they will enhance the interpretation of trial data and its presentation to healthcare professionals and policy makers. It is reasonable to suggest that a systematic review should be performed (or updated) after each and every study in the development of a new intervention and doing so will enhance decision making when deciding whether to proceed with further development, and when implementing the positive findings for a new intervention.

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FIGURE 1

Research flow diagram

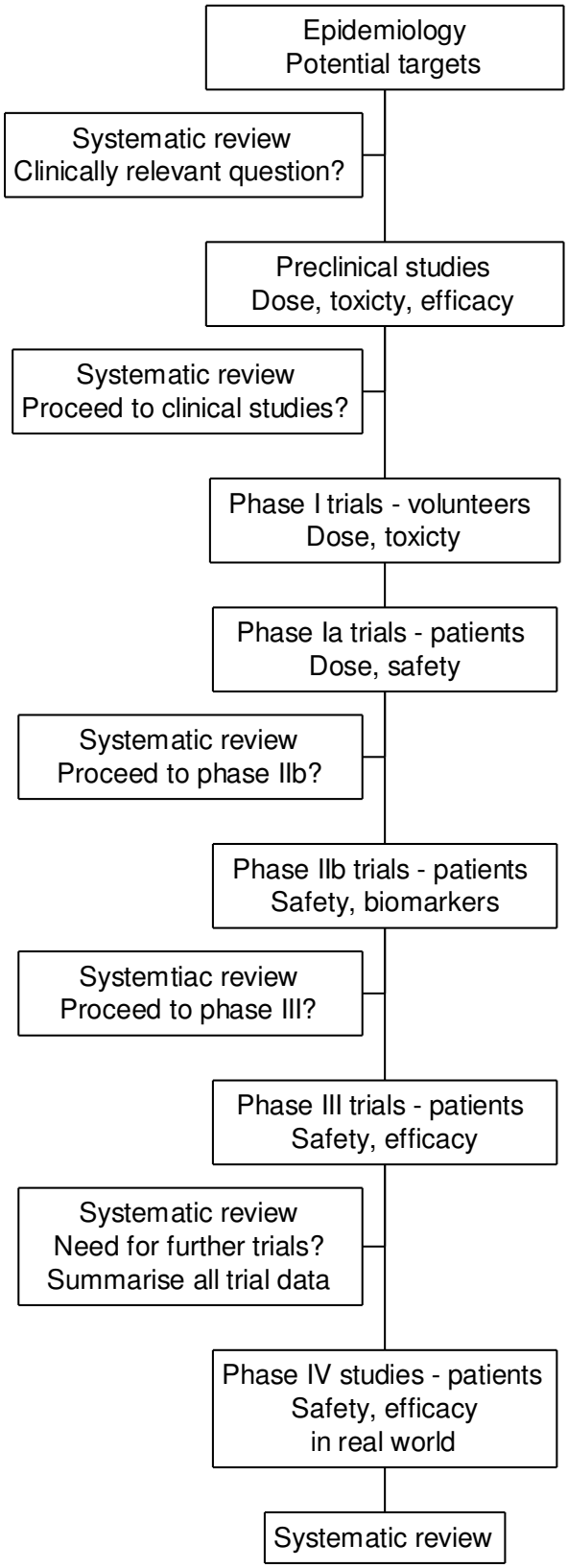

FIGURE 2

Cumulative meta-analysis plot for tirilazad versus control

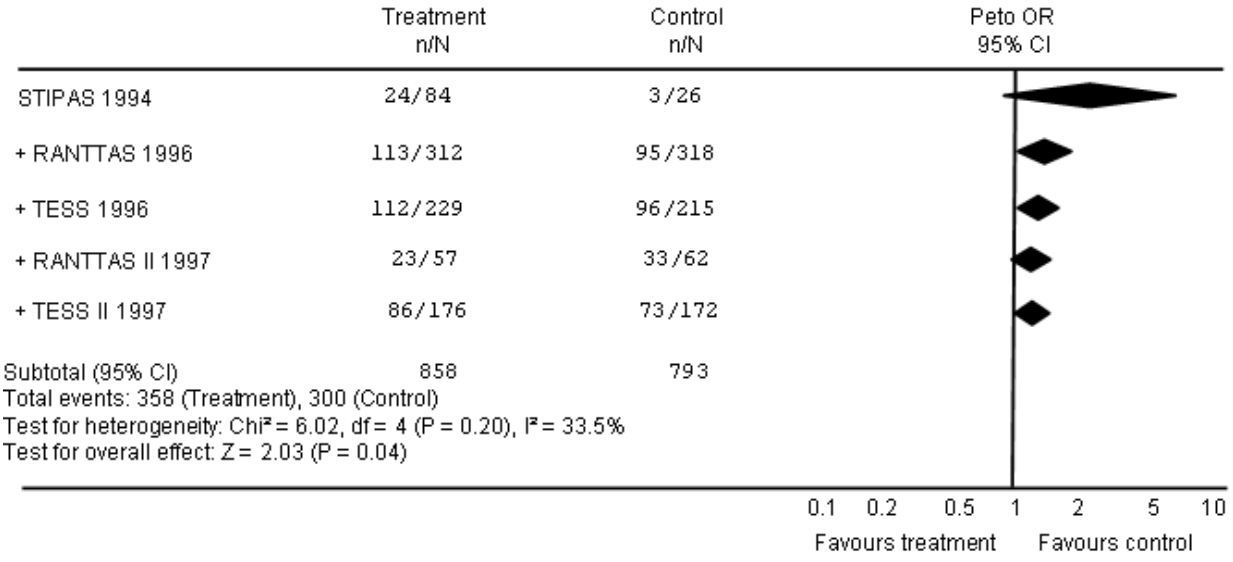

FIGURE 3

Effect of delay until first dose in minutes on total infarct volume in experimental models of transient ischaemia.[33] The size of the circle is proportional to the size of the study.