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WHAT SHOULD BE INCLUDED IN META-ANALYSES?

An Exploration of Methodological Issues Using the ISPOT Meta-Analyses

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Abstract

Objective: To explore the impact of methodologic issues on the results of meta-analyses. The following issues were examined: the type of literature search strategy used; inclusion or exclusion of non–peer-reviewed studies; the inclusion or exclusion of non-English language publications; the effect of trial quality; and the inclusion or exclusion of non–placebo-controlled studies.
Methods: The International Study of Perioperative Transfusion (ISPOT) meta-analyses were used to evaluate each of the methodologic issues. The 10 meta-analyses consisted of technologies to reduce the need for perioperative red blood cell transfusion. The number of trials for each of the meta-analyses varied from 2 to 45. Both EMBASE and MEDLINE searches were conducted, including the use of systematic search strategies.
Results: MEDLINE identified the vast majority of trials. Alone, MEDLINE would have missed 8 studies compared to 10 for EMBASE. Use of the systematic search strategies greatly reduced the number of articles to be reviewed compared to open searches. Type of publication, country of study origin, inclusion of non-English publications, and trial quality had very little impact on the estimates of effect. The use of placebo versus open-label control affected the magnitude of the odds ratio for two of the meta-analyses. The results of the two meta-analyses were not statistically significant if only placebo-controlled trials were included.
Conclusions: While methodologic issues had very little impact on the ISPOT meta-analyses, further studies are needed in a variety of other clinical settings. Because MEDLINE, coupled with a review of the references in the identified trials, identified the vast majority of trials, one needs to consider the costs and benefits of searching EMBASE and the pursuance of unpublished and unindexed trials.

Keywords: Meta-analysis, Methodology, Blood transfusion

Fleiss and Gross (14) suggested four primary uses of a meta-analysis: a) to increase statistical power for important endpoints and subgroups; b) to resolve controversy when studies disagree; c) to improve estimates of effect size; and d) to answer new questions that were not previously posed in the individual studies. For these reasons, there has been an appreciable increase in the number of meta-analyses conducted and published over the last 10 to 15 years. They are viewed by some as providing the best available estimate of the efficacy of an intervention (4). Others feel that it is inappropriate to pool data from different trials and point out instances in which the results of meta-analyses have been contradicted by subsequent large "definitive" trials (23). There is thus considerable interest in how the results of meta-analyses may be influenced by potential sources of bias stemming from the methods with which trials are pooled.

While much methodologic research related to meta-analysis has concentrated on statistical methods, issues related to data collection are equally important. In fact, the validity of the statistical analyses depends on the validity of the underlying data. Since the aim of a meta-analysis is to systematically review the evidence, it is essential to identify as many randomized trials as possible. In order to do this, a search strategy must be comprehensive, more than one database often needs to be used, the references of all eligible articles should be checked for potential studies, and it is suggested that researchers and industry representatives should be asked to identify trials (8;11;24;27;28;31;33). Some authors (12;17;25) suggest that excluding non-English language trials can effect the results of a meta analysis, since trials might be more likely to be published in an English language journal if results are statistically significant (12).

Some methodologic characteristics, such as blinded randomization, appear to have a consistent effect upon the results of meta-analyses (3;30). However, the effect of other characteristics, such as the formal assessment and incorporation of trial quality and the inclusion of non–peer-reviewed publications, is less clear (2;13;30). Some publications suggest that trial quality affects the results of meta-analyses because poorer quality trials have a tendency to overestimate the effect (20;26). It has also been argued that meta-analyses should not include unpublished data because they have not been subjected to peer review (2). Others argue that these data should be included to obtain the true effect size and to avoid publication bias related to the nonpublication of studies with negative results (5). Just as there is publication bias regarding experiments with human subjects (9;10), it is probable that studies that find methods to be important are more likely to be published than those that do not (32).

OBJECTIVE

As part of a larger technology assessment project, the International Study of Perioperative Transfusion (ISPOT), 10 meta-analyses of randomized trials have been conducted of therapies used to decrease the use of allogeneic blood transfusion in patients undergoing elective surgery (1;15;21;22). Discussions between clinicians and methodologists led us to explore the following issues: the type of literature search strategy used; inclusion or exclusion of abstracts, letters, or conference proceedings; the inclusion or exclusion of non-English language publications; the effect of trial quality upon the results of the meta-analyses; and the inclusion or exclusion of non–placebo-controlled studies.

METHODS

The ISPOT Meta-analyses

The technologies evaluated in the meta-analyses were aprotinin, desmopressin (DDAVP), epsilon aminocaproic acid (EACA), tranexamic acid (TXA), erythropoietin (EPO),

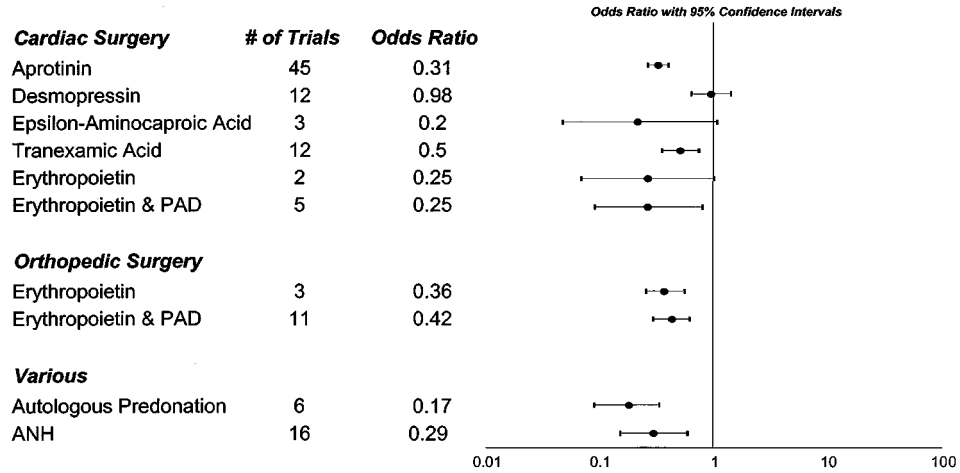

Figure 1. ISPOT meta-analyses.

autologous predonation, erythropoietin to augment autologous predonation, and acute normovolemic hemodilution (ANH). The meta-analyses of the drugs were confined to studies in cardiac or orthopedic surgery. The primary outcome used in the meta-analyses was the proportion of patients who received one or more unit of allogeneic blood. Abstracts, letters, conference proceedings, and non-English language publications were included, and a random effects model was used to calculate a summary odds ratio. The number of trials in each meta-analysis varied from 2 to 45, and the results suggested that all therapies except desmopressin and possibly EACA were effective (Figure 1).

Predeposited autologous donation (PAD) and ANH trials were not included in the evaluation of the effect of literature search strategies upon the results of meta-analyses because of the numerous keywords and search terms necessary to identify all potential trials. The consequent subjectivity and ambiguity of translating these terms from MEDLINE to EMBASE does not allow for a true comparison.

Because ISPOT involved other aspects of technology assessment in addition to these meta-analyses (e.g., cost-effectiveness), our search strategy was extremely broad. We searched MEDLINE from 1966 to April 1996, using the names of the technologies (e.g., aprotinin) as text words, and the term "human" as the only restriction. The titles and abstracts of all articles were printed and then reviewed independently by at least two individuals to identify potentially eligible randomized trials. The full texts of these articles were then reviewed independently by two individuals to determine if they were eligible for the meta-analysis. Differences were resolved by consensus. In addition, the references of all eligible trials were searched, and representatives from the companies who manufactured the therapy were asked to identify all published and unpublished studies of which they were aware. The coinvestigators from each ISPOT country were asked to approach researchers in their country who might be aware of eligible studies. Two published systematic search strategies, Haynes (18) and Cochrane (7), were also used in an attempt to limit the number of articles that needed to be reviewed. These two search strategies are based on methodologic terminology associated with randomized clinical trials and do not contain any clinical terms. Both systematic searches were modified for the OVID reference retrieval system and then translated into an EMBASE search strategy. Since both systematic searches were conducted in January 1996, the comparison between all search strategies is adjusted to that date to allow for meaningful comparisons (74 trials identified as of January 1996). All subsequent

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analyses of methodologic issues will use the total number of trials included in the published meta-analyses (74 trials + 40 trials identified after January 1996 = 114 total trials).

Exploration of Methodologic Issues

Literature Search Strategy. To evaluate the impact of MEDLINE and non-MEDLINE search strategies on the odds ratio, a subgroup analysis was performed. Non-MEDLINE trials were those identified by either industry or EMBASE and not indexed on MEDLINE.

Effect of Type of Publication. To determine whether inclusion of abstracts, letters, and conference proceedings affected the results of the meta-analyses, all trials were categorized as full journal articles, abstracts, letters, conference reports, or unpublished reports.

Country of Origin and Non-English Publications. All trials were categorized by country of study origin and language of publication in order to address their effect on the results. The meta-analysis of aprotinin was also used to evaluate country of study origin because it included a sufficient number of trials (n = 45) from a variety of countries. Any country with at least five trials was evaluated. No other meta-analysis had a sufficient number of trials to evaluate the effect of country of study origin.

Effect of Trial Quality. To evaluate the effect of trial quality upon the results of these meta-analyses, a published validated scale was used (19). The scale assesses trial quality based on randomization, blinding, and the description of withdrawals. The highest possible score is five and the lowest is zero. For our evaluation, a trial that attained a score equal to or greater than three was considered good, while a score less than three was considered poor quality. This judgment is consistent with that used in the original publication (19). Each trial was evaluated independently by two individuals, and differences were resolved by either consensus or the independent evaluation of a third party.

Placebo Versus Open-label Trials. One component of trial quality is the use of a placebo or sham in the control group. Therefore, each trial was categorized as either placebo controlled or open-label controlled.

RESULTS

Effect of Literature Search Strategy

MEDLINE identified the vast majority of published studies (Table 1). Use of MEDLINE alone would have missed 8 of the 74 (11%) studies identified as of January 1996. The rest of the studies were found by reviewing the references of articles identified by MEDLINE (two trials), or were provided by industry representatives or ISPOT collaborators (six trials). Two of the latter were published in a pharmaceutical company-sponsored symposium. EMBASE missed 10 of the 74 (14%) total studies identified as of January 1996. EMBASE missed four trials not identified by MEDLINE. EMBASE identified only two trials missed by MEDLINE, both of which were published in the journal *Perfusion*, which was not indexed on MEDLINE as of January 1996. On the other hand, a search of the bibliographies of the trials identified by MEDLINE would have identified these two trials.

The restricted search of Haynes et al. using MEDLINE missed one study identified in the unrestricted MEDLINE search, while the restricted search suggested by the Cochrane Collaboration identified all articles (Table 1). A total of 900 references in the Cochrane restricted search were identified compared to 6,263 in the unrestricted MEDLINE search.

The subgroup analyses of the efficacy of the therapies using MEDLINE versus non-MEDLINE search strategies found no significant differences in odds ratios between the two strategies (details available upon request). The largest difference in effect estimate was

Table 1. Results of Literature Search Strategies

Technology	Total studies identified (January 1996)	MEDLINE "open" search (January 1996)		"Haynes filter" MEDLINE search (January 1996)		"Cochrane filter" MEDLINE search (January 1996)		EMBASE search (May 1996)	
		Total no. of articles	No. of articles in MA (missed)	Total no. of articles	No. of articles in MA (missed)	Total no. of articles	No. of articles in MA (missed)	Total no. of articles	No. of articles in MA date-adjusted w/ MEDLINE January 1996 (missed)
Aprotinin (cardiac)	40	1,023	37 (3)	453	37 (3)	186	37 (3)	853[a]	33 (7)
TXA (cardiac)	7	458	6 (1)	344	6 (1)	171	6 (1)		6 (1)
EACA (cardiac)	1	717	1 (0)	619	1 (0)	125	1 (0)		1 (0)
DDAVP (cardiac)	11	523	10 (1)	319	10 (1)	114	10 (1)		11(0)
EPO & EPO w/PAD (ortho & cardiac)	15	3,542	12 (3)	579	11 (4)	304	12 (3)	712	13 (2)
Total	74	6,263	66 (8)	2,314	65 (9)	900	66 (8)	1,565	64 (10)

Abbreviation: MA = meta analysis.
[a] Aprotinin, TXA, DDAVP, and EACA were all combined in a single search straegy.

for TXA, where the odds ratio of the trials identified by MEDLINE was 0.57 (0.38–0.86) compared to an odds ratio of 0.50 (0.34–0.76) when all trials were used.

Effect of Type of Publication

Twenty non–peer-reviewed reports met the inclusion criteria of the meta-analyses: 15 abstracts, one letter, three conference proceedings (one also published as an abstract) and one unpublished report. Of the 20 articles, 15 subsequently appeared as full publications. Seven of the full publications reported the proportion of patients transfused, which was not in the abstract. Conversely, one full publication did not present the proportion transfused, while this was reported in the conference proceeding. Of the seven articles that reported the proportion transfused in both the full journal publication and prior reports, the results were identical in three, different in two, and indeterminable in two because the abstract reported upon a subset of patients that was described in the full journal article. Regarding differences, one abstract reported that the proportion transfused in the treatment arm was 15/48 (31%) versus 12/47 (26%) in the full publication and the proportion transfused in the control arm was 28/51 (55%) in the abstract versus 29/51 (57%) in the full publication. In the other instance, the abstract reported that the proportion transfused in the treatment arm was 81/141 (57%) versus 73/127 (57%) in the full publication and the proportion transfused in the control arm was 39/71 (55%) in the abstract versus 31/64 (48%) in the full publication.

Five–non-peer reviewed reports could be included in the meta-analyses because they had not been published as full journal articles at the time of analysis. One described the efficacy of two different technologies. Thus, six trials representing 5% of all trials were incorporated into the meta analyses. The odds ratios of the meta-analyses were not substantially changed by their inclusion (details available upon request). The largest change in effect estimate was for TXA, where the odds ratio for full journal articles was 0.57 (0.38–0.86) versus an odds ratio of 0.50 (0.34–0.76) for all trials.

Country of Origin and Non-English Publications

Fourteen of the 114 articles (13%) included in the meta-analyses were published in languages other than English (Table 2). One trial published in French reported on two technologies. Sixty-four percent of the 114 trials were from countries whose primary language is not English, 79% of which were published in English language journals. There was no statistically significant effect of country of study origin within the aprotinin meta-analysis, although the odds ratio varied from 0.12 (0.04–0.34) for articles from the United Kingdom to 0.44 (0.25–0.77) for articles from the United States (Table 3).

The odds ratios of the meta-analysis were similar whether or not non-English language publications were included, except for erythropoietin to augment PAD in orthopedic surgery, where the single non-English trial had an odds ratio of 1.00 (0.02–59.99) compared to an overall odds ratio of 0.42 (0.28–0.62). However, the small sample size ($n = 10$) and consequent wide confidence limits make it impossible to conclude that there was an effect of language of publication upon the results. It must be recognized that the small number of non-English publications in each of the analyses hampers the ability to detect meaningful differences.

Effect of Trial Quality

The 16 trials of ANH were not included in this analysis because their quality was not assessed independently by two reviewers. Of the remaining 98 trials, 52 scored greater than or equal to 3 on the Jadad scale, indicating “good” quality. There was no statistically significant effect of trial quality upon the odds ratio (Table 4). However, for TXA the poor quality studies increased the size of treatment effect by more than 50%, so that the result

Table 2. Country of Study Origin and Language of Publication

Country of study origin	Trials published	No. published in English
Australia	1	1
Austria	1	1
Belgium	3	2
Canada	4	4
Egypt	1	1
France	10	4
Germany	18	14
Israel	1	1
Italy	10	7
Japan	3	3
Netherlands	8	8
Spain	6	4
South Africa	2	2
Sweden	3	3
Switzerland	5	5
Turkey	1	1
United Kingdom	9	9
United States	27	27
United States/Australia	1	1
Total	114	100 (88%)

with all trials was statistically significant, while the result if only high-quality studies were included was not statistically significant. The effect of trial quality could not be assessed in the PAD trials because all trials were poor quality, and in EPO in cardiac surgery trials because all trials were good quality.

Placebo Versus Open-label Trials

The proportion of placebo-controlled trials varied from 0% (autologous predonation and ANH) to 92% (desmopressin) (Table 4). The odds ratios were changed in a clinically important way by the inclusion or exclusion of non–placebo-controlled studies from the meta-analyses of TXA and EPO to augment autologous donation in cardiac patients (Table 4). In both instances, the magnitude of the odds ratios changed considerably and was statistically significant when all studies (placebo-controlled and non–placebo-controlled) were used, but not statistically significant if only placebo-controlled studies were included.

DISCUSSION

Assessing the effect of methods upon the results of meta-analyses is important. One of the strengths of this exercise is that we could assess the role of a number of methodologic issues within the same technology and across a group of technologies.

Table 3. Aprotinin and Country of Publication

Country	Overall	n
Germany	0.31 (0.25–0.38)	7
Italy	0.14 (0.05–0.36)	5
United Kingdom	0.12 (0.04–0.34)	7
United States	0.44 (0.25–0.77)	6
Other	0.37 (0.27–0.50)	20
Overall	0.31 (0.25–0.39)	45

Table 4. Effect of Quality (Jadad Score) and Type of Control

Technology	All trials	Good quality (≥3)	n	Low quality (<3)	n	Placebo	n	Open label	n
Cardiac surgery									
Aprotinin	0.31 (0.25–0.39)	0.36 (0.25–0.52)	25	0.29 (0.22–0.39)	19	0.33 (0.24–0.45)	27	0.28 (0.21–0.39)	17
Desmopressin	0.98 (0.64–1.50)	0.95 (0.62–1.46)	11	4.81 (0.22–105.18)	1	0.95 (0.62–1.46)	11	4.81 (0.22–105.18)	1
ε-Aminocaproic acid	0.20 (0.04–1.12)	0.14 (0.01–1.33)	1	0.24 (0.02–3.46)	2	0.14 (0.01–1.33)	1	0.24 (0.02–3.46)	2
Tranexamic acid	0.50 (0.34–0.76)	0.63 (0.33–1.23)	5	0.37 (0.23–0.59)	7	0.63 (0.33–1.23)	5	0.37 (0.23–0.59)	7
Erythropoietin	0.25 (0.06–1.04)	0.25 (0.06–1.04)	2	—	0	0.25 (0.06–1.04)	2	—	0
Erythropoietin & PAD	0.25 (0.08–0.82)	0.21 (0.07–0.65)	1	0.26 (0.04–1.49)	4	0.45 (0.14–1.44)	3	0.04 (0.01–0.29)	2
Orthopedic surgery									
Erythropoietin	0.36 (0.24–0.56)	0.33 (0.17–0.64)	2	0.44 (0.23–0.84)	1	0.36 (0.24–0.56)	3	—	0
Erythropoietin & PAD	0.42 (0.28–0.62)	0.53 (0.31–0.89)	5	0.30 (0.16–0.57)	5	0.50 (0.30–0.84)	6	0.33 (0.18–0.61)	5
Various									
Autologous predonation	0.17 (0.08–0.32)	—	0	0.17 (0.08–0.32)	6	—	0	0.17 (0.08–0.32)	6
ANH	0.29 (0.14–0.60)	NA		NA		—	0	0.29 (0.14–0.60)	16

Abbreviation: NA = not applicable.

Different medical literature databases contain different journals. It has therefore been suggested that more than one database should be searched when doing a meta-analysis (6;8;27;28;33). In our meta-analyses, an EMBASE search did not produce a single article that was not found by either searching MEDLINE, reviewing the references of the articles found in the MEDLINE search, or contacting researchers or industry representatives. Because an EMBASE search is expensive in Canada and in France, our results suggest that an EMBASE search is not necessary for meta-analyses of therapies to decrease perioperative allogeneic red-cell transfusion. However, the proportion of articles contained in various databases likely differs depending upon the therapy, and these results cannot necessarily be extrapolated to other therapies (33). Further research in this area is needed.

On the other hand, contacting representatives of companies that produced the therapies and coinvestigators in the ISPOT countries found six articles (5% of all articles). These were mostly recently completed trials, and this effort appears to have been worthwhile. However, it may be possible that industry only let us know about the "positive" studies. We do not know how many other eligible studies we are still unaware of, and it is possible that a more aggressive, formal survey of industry and researchers may have yielded more studies. However, until it is demonstrated that this yields studies of sufficient size and quality to affect the results of meta-analyses, we suggest that our more limited approach is reasonable.

An unrestricted search strategy using only the name of the therapy and "human" can yield a huge number of publications, which are time-consuming to review. The number of studies identified can be decreased considerably by using clinical modifiers (in our case terms such as "blood transfusion"). Others have suggested that search strategies designed to identify only randomized trials have good sensitivity and specificity (5). In our meta-analyses, use of the Cochrane Collaboration search strategy (7) found all eligible trials on MEDLINE, and use of the search strategy suggested by Haynes (18) missed only one study. The use of these two search strategies greatly reduced the number of studies identified and improved the specificity of the search.

There is controversy about whether abstracts, letters, and conference proceedings should be included in meta-analyses (2;29). Those who argue that they should say that excluding them is an arbitrary act that may bias the results, while those who argue that they should not say that the studies have not undergone the rigors of peer review (2). In our meta-analyses there were relatively few abstracts, letters, and conference proceedings, and the results were similar whether they were included or not. There was no consistent trend for them to either over- or underestimate the odds ratio compared with peer-reviewed publications. It is reassuring that the data appearing in the abstracts, letters, and conference proceedings were identical to the data in subsequent full articles in all but two instances. However, some articles had not yet appeared as full publications at the time of the meta-analysis, and it is not clear if this is because recent completion of the trial did not allow enough time for publication, the investigators decided not to submit the study for publication, or the study was sufficiently flawed that publication was not possible. Other difficulties with non–full-journal publications are that they often do not provide enough information to judge the methodologic quality of the study, there is little information about side effects or secondary outcomes, and the primary outcome of interest for the meta-analysis may not be reported (e.g., an abstract may only have reported the decrease in mean number of units transfused and not the proportion of patients transfused). Six abstracts were not eligible for our meta-analyses because they did not provide information about the primary outcome of our meta-analysis, yet this information was provided in the subsequent full publications.

Most studies from countries in which the main language is not English were published in English language journals. Thus, there were relatively few eligible non-English language publications, and their inclusion or exclusion did not affect the results of any of the

meta-analyses. However, exclusion of non-English publications seems unjustifiable from a scientific point of view, and therefore they should be included in meta-analyses.

Trial quality, as measured by the Jadad scale, had virtually no effect on the results of any of the meta-analyses except that of TXA. However, we found, as have others (3;30), that there was a general trend for non–placebo-controlled trials to overestimate the treatment effect, compared with placebo-controlled studies. In two instances, inclusion of non–placebo-controlled studies converted odds ratios that did not reach statistical significance to ones that were statistically significant. This could have been due to better precision caused by the increase in sample size, or the non–placebo-controlled trials may have been biased. Both of these meta-analyses were small, containing a total of 224 and 804 patients. It is likely that the placebo-controlled trials provide the least-biased estimate of the efficacy of therapy.

The use of scales to measure trial quality is a contentious issue (16). At the heart of this contention is that an overall score can mask the effect of potentially important individual score items. The meta-analysis of EPO to augment autologous predonation in cardiac surgery can serve as an example. While overall trial quality had no impact on results, the inclusion or exclusion of trials with an open-label control did have a significant impact. Therefore, we would suggest that if quality scales are to be used, each item of the scale should be individually analyzed to identify the potential sources of heterogeneity.

While many of the methodologic issues explored in this paper did not impact the overall results of the meta-analyses, further studies are needed to critically appraise the role of methodologic issues in other clinical settings. Particularly important is the role of MEDLINE and EMBASE. The cost of undertaking an EMBASE search can be prohibitive, especially when compared with the free and convenient Internet access to MEDLINE offered by the National Institutes of Health and the National Library of Medicine. The benefit of searching EMBASE and the pursuance of unpublished and unindexed trials must be balanced with their costs.

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