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Investigating the Application of Network Meta-Analysis in Comparing the Results of Clinical Trial Studies

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Abstract

Health decisions should be according to the evidence from randomized controlled trials. These studies compare two or more effective interventions in a specific situation on the target population. When for a specific clinical problem in randomized controlled trial studies, the effect of at least three effective interventions is examined, meta-analysis can be used to combine the effect of the interventions and obtain a general estimate of that effect size in the target population; while for most clinical conditions, and there are more than two effective interventions. In such a situation, multiple meta-analyses are not possible. In addition, direct clinical trials may not have been introduced and used for all interventions. Network meta-analysis is a method to compare several interventions simultaneously in a single study by the combination of indirect and direct evidence in a network of randomized controlled trials, the findings of which provide the possibility of ranking different interventions. The current study was prepared with the aim of providing basic explanations regarding the benefits of producing a network based on indirect and direct evidence, conducting network meta-analysis, checking the main assumptions, and the stages of analysis.

Keywords: Meta-analysis, Clinical trial, Randomized controlled, Network

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Introduction

The decisions that are made in connection with choosing the best treatment method should be based on all the evidence. This evidence is usually provided through randomized controlled trials (RCT), which is the most complete type of intervention study, comparing two or more interventions for a specific condition affecting a specific target population [1-3].

If at least three different intervention methods are available in the studies related to a specific clinical problem, it is possible to use meta-analysis to combine several studies and obtain a general estimate of the desired specific treatment effect. Target population used. To assess clinical effectiveness, relative effects estimated for RCT treatments are combined using methods that preserve randomization within each study. However, for most treatment conditions there may be more than two appropriate interventions. In such cases, conducting multiple meta-analyses in pairs (comparison of two interventions at the same time) or any therapeutic intervention to compare with the control group creates limitations for practical, consistent, and transparent decision-making [4, 5]. However, by looking at several trials that have been conducted separately for different pairwise comparisons in a given clinical setting, it is important to decide on the best intervention. It is also clear that often for all comparisons, RCTs have not been conducted [4, 6].

Network meta-analysis has benefits over meta-analysis of two-by-two interventions, which include the ability to clarify conflicting results from multiple studies with several common comparators and perform indirect comparisons in clinical trials. In addition, network meta-analysis provides the possibility of increasing statistical power and cross-validation by using appropriate network design and sufficient sample size. Like traditional meta-analysis, the network meta-analysis validity is also based on two important principles: the first is the quality of the evidence and the second is the similarity between the clinical trials included in the network [7-9]. The quality of evidence depends on many internal and external factors. In terms of internal factors, when preparing a network meta-analysis, a systematic review should be used to identify related studies. Using a systematic review ensures that there is no bias in the selection of studies [10, 11].

In general, to form a network meta-analysis, studies are needed in which at least three effects of different intervention methods have been examined on a specific clinical problem, and the comparisons made in these studies are such that at least two There is a direct relationship between these three different intervention methods. Network meta-analysis follows all the challenges found in a standard meta-analysis, but as the complexity of network meta-analysis increases due to the multiple comparisons involved, inconsistency or incoherence may arise in the model. Therefore, it is necessary to examine assumptions such as similarity, homogeneity, and compatibility between researchers using valid evaluation methods [12-14]. The purpose of this research was to show the complete process of conducting a network meta-analysis study.

Materials and Methods

A network meta-analysis in the systematic review is a meta-analysis in which more than two interventions are performed using both direct comparisons (comparisons within an RCT) and indirect comparisons (comparisons with RCTs that share a common comparator). For example, in an RCT comparing A and B treatments, direct evidence is related to the relative effects between A and B, and indirect evidence is related to the evidence acquired through one or more common comparators. In other words, in the lack of RCTs that directly assess A and B, interventions A and B can be indirectly compared. If both studies are compared with C (forming an A-B-C evidence loop), the closed loop is related to the part of the network in which all interventions are connected directly by forming a closed geometric shape (e.g. square, triangle). In this case, there is both indirect and direct evidence. Open or non-locked loops are incomplete connections in the network [12, 15].

The purpose of forming a network of interventions and comparing RCTs with each other is to produce consistent estimates of the relative effects of each intervention compared to others using direct and indirect evidence. However, the main question is whether the studies in the network have reached enough similar and meaningful results from direct and indirect comparisons or not.

Results and Discussion

Search strategy and quality assessment of studies

The selection of articles used in network meta-analysis is done using the Preferred Reporting Items for Systematic PRISMA (Meta-Analyses and Reviews) recipe and considering the necessary Participants, Interventions, Comparators, and Outcomes (PICO) [16, 17]. After screening the studies based on the exclusion and inclusion criteria, the desired information is extracted. Most of the entry and exit criteria are chosen in such a way as to adjust the influencing variables in the network, among which the characteristics of the population under investigation, age, gender, study design, and various other things can be mentioned.

Assessing the bias risk and investigating it in a network meta-analysis is far more challenging than traditional meta-analysis; because the main difference between network meta-analysis and traditional meta-analysis is that a traditional meta-analysis only results in the estimation of one effect size, while a network meta-analysis more different studies are included in the network and more than one effect size is reported [18, 19]. Bias risk is related to the problems with the design and implementation of single clinical trials that raise questions about the validity of their findings. Among the various tools for assessing the quality of single RCT studies, the Cochrane group's standard risk of bias tool, which categorizes and reports studies into three categories of low bias, high bias, and unclear bias, is more widely used than others [10].

Establishing the assumptions raised in a network meta-analysis makes the results of indirect and direct evidence reliable and meaningful. Among the assumptions that should be examined are the assumption of homogeneity, the assumption of compatibility, and the assumption of similarity.

Homogeneity assumption

Usually, in a meta-analysis, the results of several RCTs comparing the same interventions A and B are used to estimate the relative effect, and the difference between these results may affect the final effect for comparing two interventions A and B. These differences may have a clinical or methodological origin, each of which causes statistical heterogeneity [20]. To evaluate the degree of heterogeneity, traditional meta-analysis methods such as I2 and Q criteria are used [21]. Investigating the origin of heterogeneity through subgroup analysis is one of the ways to deal with statistical heterogeneity in studies. Conducting network meta-analysis using random models and meta-regression models is one of the other ways to deal with heterogeneity among studies.

Assumption of similarity

The studies that are included in the network meta-analysis should be comparable according to the effect size they have examined and the characteristics of the patients that can affect the effect of the treatment. This hypothesis means that if C performs better than B, and B performs better than A, then C must perform better than A. This assumption is established when the research is comparable according to the stated characteristics [22]. In some research, the similarity hypothesis is referred to as the transitivity hypothesis.

Due to the lack of scientific and valid methods to check or improve the assumption of similarity between studies, the proposed tests are often used to check the assumption of homogeneity [23], which may be considered informal and subjective.

Compatibility assumption

When direct and indirect evidence are combined, there must be no discrepancy between these evidences. For example, the relationship between B and C can be obtained from the direct comparison of treatment B and C, and it can be obtained indirectly from the tests AB and AC, in which case there should not be a significant difference between the results of these two ways. Consistency only applies to closed loops of evidence. For example, it does not make sense to say that the comparisons AC are compatible with AB. It can only be said that the values of BC, AC, and AB are consistent [24]. Boucher's method and node splitting method can be mentioned among the widely used methods in investigating inconsistency within a meta-analysis network [25].

Analytical methods of network meta-analysis

Network meta-analysis can be done in the form of fixed or random effects models. In a fixed effects model, it is assumed that there is no difference between the effect sizes of different interventions in studies for a two-by-two comparison, and the differences that may be observed for a particular comparison among research results are only due to chance. If there is heterogeneity, existing differences can be controlled using random effects models [20].

Effect size estimation methods in network meta-analysis

In network meta-analysis, each of the defined models can be performed in a classical or Bayesian framework.

The classical approach calculates the probability of interventions while the observed data have occurred under a specified distribution such as a normal distribution with assumed parameters. The analysis results are presented as effect size (such as mean difference, relative risk, and odds ratio) with a 95% confidence interval, similar to the meta-analysis results for each intervention pair [26].

The classical approach is a method that is usually used to perform network meta-analysis and includes weighted averages and confidence intervals for the estimators of each of the fixed and random effects models. The Bayesian approach combines the likelihood function and the prior probability distribution to acquire the posterior probability distribution of the parameters as well as a simple way to estimate them together. The results are often presented as a point estimate with a 95% confidence interval, which is generated using MCMC (Markov chain Monte Carlo) simulations [27]. The Bayesian method has a suitable framework for choosing the best treatment and estimating the probability of all of them, and it can rank treatments based on their effectiveness.

How to interpret the results of network meta-analysis

Network meta-analysis articles typically report two sets of outputs, the effect sizes of pairwise comparisons and treatment rankings. The effect size of pairwise comparisons is estimated from all relevant evidence in the network along with confidence intervals for each, whose interpretation can help better decision-making.

A list of effect sizes for all pairs contains useful information, especially when one of the treatments is compared to a reference treatment such as a placebo or standard treatment. The explanation of the results is similar to the traditional meta-analysis, which is presented in the form of pairwise comparisons and specifies the status of each treatment relative to each other. Tree diagrams also graphically report the values of effect sizes and their confidence intervals [28]. Another output is the probability of ranking treatments. A detailed ranking report may include statistical indicators such as median ranks with confidence intervals, Rankogram, and the surface under the cumulative ranking curve (SUCRA) [12].

Due to the lack of an overview of methodological challenges in different fields for research to conduct a network meta-analysis and the importance of network meta-analysis in clinical decision-making, the current study was conducted to provide a general summary of the most important issues in conducting a good network meta-analysis should be done.

Meta-analysis is considered one of the highest sources of scientific evidence, but it can be misleading if not done correctly. Statistical methods to blend the results of individual studies in a systematic review can introduce utilitarian information for clinical decision-making. To decrease the error and ensure the accuracy of the results from meta-analyses (either network meta-analysis or standard meta-analysis), a systematic review must be designed and implemented accurately [29]. Aspects of conducting and designing a systematic review include introducing review questions, specifying eligibility criteria, searching and choosing studies, evaluating the bias risk and evidence quality, performing meta-analysis, and reporting and explicating findings [30].

When more than two interventions are considered, analysis of clinical trials using network meta-analysis ensures that all relevant evidence (whether direct or indirect) is used to produce consistent estimates of the effect sizes of each intervention compared with other items included in the modeling. This will make more efficient use of evidence and increase estimates. In addition, since several different sources are used to derive evidence, the final estimates are more robust than if only direct sources were included in the modeling [31].

By evaluating important assumptions such as similarity, compatibility, homogeneity, and their modification, in the implementation of network meta-analysis, it is assumed that there are no studies involved in the network or characteristics of these researches that can determine the relative effect of the interventions when compared with others. Interventions are compared, affect. Therefore, careful examination of these assumptions is very important so that the research ultimately leads to reliable results [29].

The acceptance rate of network meta-analysis in the medical community depends on how methodological research is conducted, the evidence validity, and the facility of interpretation for decision-makers. In addition, collaboration between statisticians, clinicians, epidemiologists, and others is necessary to develop, implement, and evaluate network meta-analysis methods; because it leads to the development of this useful method in various clinical fields.

Conclusion

Network meta-analysis is a promising method that can conduct comparative effectiveness studies in the presence of several treatments, but caution should be taken when by this method. Clinical questioning should be conducted using either subject area clinical experts or a statistician. In addition, before conducting network meta-analysis, it is necessary to check the validity of resource commitment to make a flexible assessment and ensure the validity of network meta-analysis results. Good reporting and interpretation are also important for a network meta-analysis to be properly evaluated.

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