Network meta-analysis

Metaanálisis en Red

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Abstract

Network meta-analysis (also called mixed treatment comparisons) is a powerful statistical technique that combines different studies to perform the analysis of multiple treatments or to estimate an indirect effect in the absence of a direct comparison. These studies are carried out through the development of a network analysis, allowing the estimation the relative effects of all the treatments or interventions included in the network simultaneously and using techniques that estimate the direct and indirect evidence analysis. Inductions are comparisons of different treatments using data from different studies and using a common comparator, either because these studies are not available or are of poor quality, or if one wishes to compare numerous alternatives. In network meta-analysis, the mixed treatment comparison is based on a closed-loop network, which provides much more information and has less bias than open-loop models. Currently in closed-loops or cycles, several statistical methods are used for their analysis, but in each study, a unique statistical approach is used. The most frequent to date are the Bayesian methods, therefore, it is more important the analysis of the research process and network than obtaining a single weighted final measure. The objective of this narrative review is to describe the fundamental concepts of network meta-analysis, their usefulness and methodological considerations, the fundamentals of the analysis, the network conformation and its main limitations.

Key words: Network meta-analysis. Indirect comparisons. Mixed treatment comparisons. Multiple treatment comparison. Meta-analysis.

Resumen

El metaanálisis en red (también llamado comparaciones mixtas de tratamientos) es una poderosa técnica estadística que combina diferentes estudios para realizar el análisis de tratamientos múltiples o estimar un efecto indirecto en ausencia de una comparación directa. Estos estudios se realizan mediante el desarrollo de una red de análisis, lo que permite calcular los efectos relativos de todos los tratamientos o intervenciones incluidos en la red simultáneamente, utilizando técnicas que estiman los análisis directos e indirectos de la evidencia. Las comparaciones indirectas son comparaciones de diferentes tratamientos utilizando datos de distintos estudios mediante un comparador en común, ya sea porque no existen estos estudios o son de baja calidad o bien porque se desea comparar numerosas alternativas. En el metaanálisis en red, la comparación mixta del tratamiento está basada en una red de bucles cerrados. Estos proveen mucha más información y está menos sesgada que la de los bucles abiertos. Actualmente, en los bucles o ciclos cerrados se utilizan varios métodos estadísticos para su análisis, pero en cada estudio se utiliza un enfoque estadístico único. Los más frecuentes hasta la fecha son los métodos bayesianos. Por lo tanto, es más importante el análisis del proceso de investigación y la red creada que la

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obtención de una medida única ponderada final. El objetivo de esta revisión narrativa es describir los conceptos fundamentales de los metaanálisis en red, su utilidad, las consideraciones metodológicas, los fundamentos del análisis, la conformación de la red y sus principales limitaciones.

Palabras clave: Metaanálisis en red. Comparaciones indirectas. Comparación de tratamientos mixtos. Comparación de tratamientos múltiples. Metaanálisis.

Introduction

Any person that faces the task of making a health decision that affects millions of people or that entails important health risks, wants their decision to be as objective as possible and based on the best available evidence. In practice, this usually means finding and combining the results of different investigations and looking for the best alternatives for health intervention. This decision process is dynamic over time, since the number of health interventions available to solve a health problem increases over the years and, in many areas of medicine, very quickly. This forces to have an analysis structure that incorporates all the existing alternatives for a topic and in which; in addition, new alternatives are incorporated every year, making possible to always be clear about the differences between all the alternatives. This is a network analysis that grows over time. As a result, in recent decades, network meta-analysis have been developed, which are statistical techniques that allow combining different studies with the same or different treatments sets to create a global analysis. This is done through the development of a network analysis that allows the estimation of the relative effects of all the treatments included in the network. These effects are estimated using both direct and indirect analyses between treatments¹⁻⁵.

In recent decades it has been generally accepted that well-designed, controlled clinical trials provide the best evidence for decision-making, the most rigorous and valid evidence related to the relative effects between different interventions. When searching the available evidence for decision-making, it is common to find more than one controlled clinical trial: increasing the level of information can increase the level of precision to make a decision. The studies can be pooled using the technique of a systematic review, which allows, through a rigorous protocol, to improve the selection of studies according to their methodological quality. When the design of the studies allows it, the available results of several of them can be pooled in a quantitative way, through data meta-analysis, and thus obtain a more precise estimator by increasing the number of patients by mathematically pooling the studies. The direct

comparison (intervention vs. placebo, etc.) of treatment alternatives in controlled clinical trials, also called direct analysis, is the most reliable way of comparing treatments¹⁻⁵, but as the number of available treatments increases, the number of possible comparisons between them increases exponentially. Few clinical trials compare four or more different interventions in the same study, as this greatly increases their cost. Most often, there are controlled clinical trials for only a small fraction of the possible interventions to be compared (usually two or three interventions). In addition, the new treatments that are developed are evaluated by performing controlled clinical trials that in general compare the new treatment only with some of the existing alternatives and not with all of them. The gold standard is usually chosen, or the most relevant competitor in the market, which increases the lack of direct comparisons between the intervention alternatives as the years progress. This is because there is no incentive for the companies that develop new technologies to invest resources in comparing all the existing alternatives, therefore, companies only evaluate the alternatives that in their opinion offer greater economic benefits. This gap in the lack of comparisons is not only far from being resolved but it is going to get much worse in the future.

From the point of view of the techniques used in evidence-based medicine, when there is no controlled clinical trial comparing the alternatives directly, a study with a lower level of evidence is used. The quality of the evidence decreases to descriptive observational studies or even to case series and opinions of experts, seeking the best evidence to make a decision, since there is not an ideal direct comparison. However, is this the right thing to do? When there is no direct comparison between two treatments, the following dilemma is generated: What is better, to make a decision with a case series or an opinion of experts, or to estimate mathematically what would be the indirect comparison, through the direct information that does exist, between the different studies? In these cases, an indirect comparison between treatments through a network meta-analysis obtains important information for decision-making, which complements the available information^{1,5}.

Health decision-making is based at least on the results and the costs of the interventions involved. Therefore, they involve mathematical models of multiple alternatives, typical of economic analysis. Decision trees and Markov chains are the most commonly used in cost-utility or cost-effectiveness studies. In these investigations, network meta-analysis are very useful, since they provide the probabilities incorporated in the models to perform these multiple analysis¹.

For example, conducting a study to identify which ocular hypotensive drug is more effective in reducing ocular tension in the treatment of patients with chronic open-angle glaucoma, involves the comparison of 9 different medications⁶. When performing a systematic review, we selected controlled clinical trials, and the limiting factor is the comparison of three or fewer hypotensives simultaneously. If a meta-analysis is performed, the comparisons can only be made with 2 treatments in each analysis: the relative risk (RR) analyzes 2 alternatives simultaneously; therefore, we cannot obtain the relationships among the 9 available treatments. To perform an economic analysis study incorporating the costs to know which treatment has a better cost-effective relationship, one must incorporate the probabilities in a decision tree model, which forces to estimate the relationships between these 9 treatments through a network meta-analysis. This allows running the model and complementing the pre-existing information for decision-making.

Lumley proposed the concept of network meta-analysis in 2002². He provided a unified statistical framework for the comparison of multiple treatments. Until 2005, the number of online meta-analysis articles was minimal. Since 2006, there has been an exponential increase in this type of studies: hundreds of studies of this type are carried out each year and are increasingly used as sources of estimation. In the absence of direct analysis in some medical areas, international evaluation agencies (National Institute for Health and Care Excellence [NICE] in the United Kingdom, Canadian Agency for Drugs and Technologies in Health [CADTH] in Canada, Pharmaceutical Benefits Advisory Committee [PBAC] in Australia, Haute Autorité de Santé [HAS] in France, Institute for Quality and Efficiency in Health Care [IQWiG] in Germany, or even the International Society for Pharmacoeconomics and Outcomes Research [ISPOR])¹, consider that indirect comparisons are a source of information in health decision-making, for which each agency has published its own standards in this regard. There is

also an extension of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA), the PRISMA-Network Meta-analysis (NMA), which allows guiding the analysis of studies in a more structured way⁷. Therefore, it becomes increasingly necessary to understand this type of studies and know how to interpret their results.

The objective of this narrative review is to describe the fundamental concepts of network meta-analysis, their usefulness, the network conformation, methodological considerations and its main limitations.

What is a network meta-analysis?

The meta-analysis in a network (network meta-analysis)¹⁻⁵, is a statistical technique that combines experimental studies with similar characteristics that have not been directly compared through the application of a network analysis. This integrated and unified analysis incorporates all the information of direct and indirect comparisons on the different treatments and allows the estimation of the relative effects of all the treatments included in the network. They are estimated using both direct and indirect analyses (Fig. 1).

It is called «direct comparison» when 2 treatments have been evaluated (A vs. B and A vs. C) one against the other, and «indirect comparison» if two treatments have never been directly compared against each other (B vs. C), but these two treatments have been compared against a common comparator (A, placebo): an indirect comparison between treatments can be made using the relative effects of the two treatments versus the common comparator. In figure 1, each node (circle) reflects an intervention or comparator (placebo, treatment, etc.) and the line connecting two nodes reflects one or more clinical trials. In some diagrams, the size of the node is changed to represent the greater or lesser importance of the study and a thicker or thinner line can be drawn to visually represent if it is one study or many⁸⁻¹⁰. Although it is often argued that indirect comparisons are only necessary when direct comparisons do not exist, it is important to bear in mind that the results of indirect tests combined with direct tests can reinforce the evaluation between treatments^{11,12}. Indirect estimates provide an additional estimate of the treatment effect that complements the direct estimate. In some cases, direct estimation may come from the comparison of controlled small-scale clinical trials or with some methodological problems, while the indirect comparison may come from the comparison of

Figure 1. Direct, indirect and mixed comparisons.

controlled clinical trials of very good quality and be more consistent and efficient than the direct estimate.

Network conformation

A network is composed of at least three nodes connected by lines. There are two different types of networks that show how treatments are compared: open-loop and closed-loop (Fig. 2)^{1,2,11,12}. They are related to the number of studies with direct comparisons that exist between the different alternatives. «Closed-loop» refers to when there is at least one study that compares one alternative with another and allows all the alternatives to be connected to each other in the network diagram (Fig. 2 C). Open-loop means there are no direct comparisons (Fig. 2 A and B). In open-loop networks, the relative effect between B and C is compared (Fig. 2 A) by means of an indirect comparison anchored to A (in the references it is also called «adjusted¹»). It is fundamental in the comparison that the randomization is not broken^{8,13,14}, so the data of the treatment groups should not be used alone and hence generate the comparisons omitting the control or anchored group. When this type of comparison is made, it is called «simple indirect comparison»

and generates bias: it should not be done. Relative effects must be compared to preserve the randomization by comparing the probability ratio of B vs. A with the probability ratio of C vs. A^{1,14}. When there are multiple treatments around a control group (Fig. 2 B), it is also referred to as «star-shaped network». In this case, not all clinical studies have the same comparator or anchor (B vs. E), but all interventions must remain connected to each other.

Mathematically, in closed-loops, for each comparison of two alternatives, there are 2 sources of information: the estimates of the effect obtained both directly and indirectly (Fig. 2 C). In these cases, the network is called «mixed treatment comparison». In practice, very large networks with many alternatives are usually a mixture with zones of both loops (Fig. 2 D).

When there is an open-loop, the risk of estimation bias is greater than when there is none. When both direct and indirect tests are available, the two sources of information can be pooled as a weighted mean. This type of comparison can be extended to «k» comparisons, to facilitate simultaneous inference on all available treatments and provide more information on the selection of treatment options or interventions^{11,12,14}. Even when the results of direct comparisons are conclusive,

Figure 2. Types of meta-analysis networks. Left: open-loop network examples; right: closed-loop. In the bottom, the differences for comparisons between studies for A and C networks is depicted.

when combined with the results of indirect estimates in a mixed treatment comparison, a more accurate estimate for the interventions can be obtained. In addition, the population from which the results are inferred is broadened. All the loops are used to perform the analysis, but the further away the loops are from the estimate that is being calculated (that is, the estimate is derived from a more distant indirect analysis within the network), the lower the weight at the calculated indirect estimate these loops have^{11,12}. Finally, in the calculations obtained, there must be consistency between direct and indirect estimates with closed-loops, that is, the directly estimated value must be similar to the indirectly estimated value. If this does not happen, it is called “inconsistent estimations” and, therefore, the estimates must be interpreted with great caution until the cause of the difference is identified. In these cases, we should proceed in a similar way as in a typical meta-analysis: if the sources included in the analysis meet the appropriate quality criteria of a controlled clinical trial, the inconsistent estimates show the uncertainty of the estimate or the true heterogeneity of the study populations related to the effect of the treatment. The challenge is not choosing between direct or indirect estimations but rather the

adequate characterization of that uncertainty to facilitate the decision-making process.

Limitations

The obtained indirect comparison is not directly randomized, as in the case of direct comparisons. It is observational, which is why it is subject to more potential bias than direct comparisons^{1,11,12}. In well-conducted and randomized controlled clinical trials, estimations with minimal effect bias are obtained. Theoretically, when these are used to generate an indirect estimate, the calculated estimate is also almost unbiased. However, in practice, controlled clinical trials are usually not methodologically identical and the indirect comparison depends on the assumption of similarity or transitivity of the studies¹⁴: if treatment B is better than A, and A it is better than C, it is assumed that treatment B is better than C (Fig. 1). Nevertheless, there are studies that discuss the non-compliance of transitivity, since it does not always occur⁸. This assumption depends on how similar the methodologies are, on the pooling of very old studies with new ones, on groups of patients, etc. In these aspects, network meta-analysis are not very

different from normal meta-analysis; both require a systematic and exhaustive search of all potentially relevant articles, the selection of the articles by explicit and reproducible criteria that will be included, the description of the design and similar conductance of the original studies, the summary of the data obtained and results (outcome) measured in a similar way. Therefore, the results interpretation takes into account the research process and the network more than the summarized mathematical measure obtained. All this process has the potential risk of producing bias in the study and, thus, yielding invalid conclusions^{1,2,11,12,14}. Song, et al.¹³ estimated the inconsistency of network meta-analysis between direct and indirect comparisons measured by the estimated odds ratio (OR). This was statistically significant in 14% of the cases (CI 95%: 9-22). Veroniki, et al.¹⁵ found in 2013, inconsistency in the results in 2 - 9% of the cases, depending on the measure of the effect and the estimation of heterogeneity. In both studies, it is estimated that consistency is of around 85% of the cases¹⁶, that is, that the estimates obtained indirectly and those obtained directly coincide in 85% of the studies evaluated.

Although network meta-analysis are generally recommended only for randomized controlled trials, the methodology of network meta-analysis could be applied to situations in which data are obtained from other types of research.

Methodological considerations

Several statistical methods are used to perform the estimations in network meta-analysis^{11,12}. They can be done with models of frequentist approaches of fixed or random effects, meta-regression models or Bayesian models, among others. Some approaches provide greater flexibility than others when adjusting for covariates and analysis of multiple interventions. Most network meta-analysis use a unique statistical approach. The most frequent is the Bayesian model. The performance comparison of the different methods has not been thoroughly studied. Future methodological studies may evaluate the usefulness and robustness of the various statistical methods and determine the circumstances in which a specific method is more efficient and appropriate than another.

Statistical software

The most used programs for the analysis of the different models and their graphic representation are WinBUGS, OpenBUGS, JAGS (Just Another Gibbs

Sampler), SAS® (Statistical Analysis System), STATA® (with MV_META command)⁹, R (with metaphor, GeMTC, pnetmeta and netmeta packages)¹⁷ and Excel¹⁸. They allow programming for such purposes through different analysis commands and graphic representations available. The management of these programs requires vast statistical knowledge to create and run the analysis models in networks.

Conclusions

Network meta-analysis is a very useful type of research to compare multiple treatments or when there is a lack of direct comparisons between treatments. Its use is complementary to direct evaluations when they exist; it does not substitute them in any case. If indirect comparisons come from closed-loops, they provide much more information and have less bias than open-loops. Network meta-analysis can be very informative and useful, but, given the assumptions used, confidence in the overall estimate is not always high. The statistical methods suitable for each type of analysis and the development of computer programs that allow automated and safe analysis are still to be defined. Consequently, currently the analysis of the process and the network of interventions are more important than obtaining a final weighted measure.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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Conflict of interest

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