Technical Note

Network meta-analysis: an illustration

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Abstract

Network Meta-analysis (NMA) is a generalization of pairwise meta-analysis that permits multiple comparisons (three or more treatment groups) in a single analysis. It includes both direct comparisons of treatments which have been compared head-to-head and also indirect comparison of treatments that have not been compared head-to-head, but do possess a common comparator thus accounting for a broader evidence base. A pairwise meta-analysis results in a single pooled estimate, whereas a NMA leads to the computation of several such estimates. The present article illustrates the procedure of NMA by including a simple practical example.

KEY WORDS: Meta-analysis, network meta-analysis, indirect comparison, direct estimates, indirect estimates

Introduction

"Network meta-analysis (NMA) can be defined as the simultaneous comparison of multiple competing treatment modalities within the framework of a single statistical model."[1] It is a generalization of pairwise meta-analysis that permits multiple comparisons (three or more treatment groups) in a single analysis. It includes both direct comparisons of trials comparing the treatments head-to-head and indirect comparisons of treatments that have not been compared directly but possess a common comparator.[2] For example, the studies that have compared treatments X versus Y and Y versus Z are used to indirectly compare interventions X versus Z.[3] Most of the randomized-controlled trials (RCTs) compare the active treatment against a placebo. The trials comparing the active treatments head-to-head are less frequent making it difficult for the clinicians/medical practitioners to recommend the best-available treatment. Under such situations, NMA is an alternative choice to indirectly obtain estimates for head-to-head comparisons of active treatments considering the placebo as the common comparator.[4] NMA has, hence, come into prominence within this context of decision making by clinicians/medical practitioners. With this growing popularity of NMA methods and its increased usage, we felt it is not only important for medical researchers to know how it is done via statistical packages but also how the final estimates are obtained. The aim of this article is to provide a simple step-by-step tutorial on how to conduct a network meta-analysis or an indirect comparison. The other methodological details and assumptions of NMA can be found elsewhere.[5]

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Materials and Methods

The first step of NMA is the construction of network plot, which is a mapping of the treatments that have been directly compared and the treatments that need to be indirectly compared using the evidence from direct comparison. A network plot can either be an open loop or a closed loop.[6] NMA involves computation of three types of estimates, namely: direct estimates—the estimates of treatments that have been compared head-to-head are pooled together and are referred to as direct estimates. Indirect estimates—for instance, consider three treatments X, Y, and Z. Suppose there are studies having compared X versus Y and Y versus Z. In such a case, the treatment Y is considered as common comparator and estimate for X versus Z is obtained indirectly as the ratio (or difference in log scale) of the direct estimates of X versus Y and Y versus Z. Mixed estimates—the direct and indirect estimates are pooled together as a weighted average to obtain mixed estimates.[7] At this stage, it is necessary to check for the consistency, that is, the agreement between the direct and indirect estimates for a

particular comparison.[7] Presence of consistency between the direct and indirect estimates of a comparison is confirmed by Bucher method, which involves computing the inconsistency factor (IF) as the ratio (or absolute difference in log scale) of its direct and indirect estimates. Statistical significance of IF, under the null hypothesis IF = 0, is tested using Z statistic. If the confidence interval (CI) of IF captures zero, this confirms the existence of consistency between the direct and indirect estimates. It is important to note that computation of mixed estimates is possible only in a closed loop. In case if the loop is open, we may have to restrict ourselves to indirect estimates.[8]

Data

The data for the present exercise have been obtained from the systematic review "Incident diabetes in clinical trials of antihypertensive drugs."[9] The objective of the review was to assess the effects of five antihypertensive drugs, namely: angiotensin receptor blockers (ARB), angiotensin converting-enzyme (ACE) inhibitors, calcium-channel blocker (CCB), beta-blocker (BB), and diuretics on incident diabetes. Consequently, 22 RCTs were included in the review. The network plot showing all possible comparisons has been depicted in Figure 1.

Circles in the network plot are referred to as nodes. They represent the treatments being compared. The size of the nodes depends on the number of subjects receiving the treatment. The lines are referred to as edges, which represent direct comparisons. The thickness of the lines represent the number of studies under the comparison.[10]

In this article, the NMA is illustrated in the loop ACE–BB–CCB, considering BB as the common comparator with random effects model, inverse variance approach, and odds ratio (OR) as the effect measure. The data for ACE–BB–CCB loop are presented in Table 1.

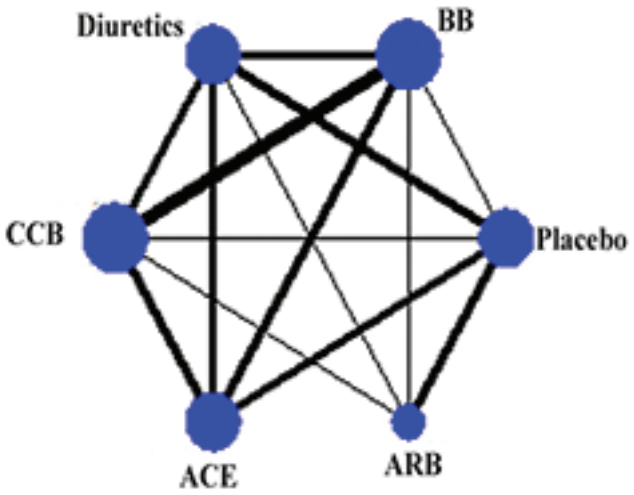

Figure 1: Network plot

Table 1: Data for the loop ACE–BB–CCB

Event1	Total1	Event2	Total2	Arm1	Arm2
70	405	45	410	BB	ACE
70	405	32	202	BB	CCB
32	202	45	410	CCB	ACE
154	3954	119	4096	CCB	ACE
799	7040	567	7072	BB	CCB
380	5230	337	5183	BB	ACE
665	8078	569	8098	BB	CCB
251	5059	216	5095	BB	CCB
97	1960	93	1970	BB	ACE
97	1960	95	1965	BB	CCB
95	1965	93	1970	CCB	ACE

Event1, number of events in the first arm; Event2, number of events in the second arm; Total1, number of subjects in the first arm; Total2, number of subjects in the second arm.

Practical Exercise

Step-by-Step Procedure for the NMA

Step 1: Compute the direct estimates for the comparisons ACE versus BB, CCB versus BB, and ACE versus CCB

Perform separate pairwise random effects meta-analysis for the comparisons ACE versus BB, CCB versus BB, and ACE versus CCB. The results of the three pairwise meta-analyses are presented in Table 2.

Step 2: Compute indirect estimates for the comparison ACE versus CCB based on estimates from the comparisons ACE versus BB and CCB versus BB

$$\ln OR_{ACEvs.CCB,indirect} = \ln OR_{ACEvs.BB,direct} - \ln OR_{CCBvs.BB,direct} = -0.18 - (-0.21) = 0.03$$

$$\begin{aligned} Var(\ln OR_{ACEvs.CCB,indirect}) &= var(\ln OR_{ACEvs.BB,direct}) + var(\ln OR_{CCBvs.BB,direct}) \\ &= 0.01 + 0.01 = 0.02. \end{aligned}$$

$$SE(\ln OR_{ACEvs.CCB,indirect}) = \sqrt{var(\ln OR_{ACEvs.CCB,indirect})} = \sqrt{0.02} = 0.13.$$

Here, variance of an estimate can be obtained from the corresponding confidence interval as [(upper limit–lower limit)/(2*1.96)]2.

Table 2: Direct estimates

Comparison	lnOR (95% CI)	OR (95% CI)
ACE vs. BB	–0.18 (–0.40, 0.04)	0.84 (0.67, 1.04)
CCB vs. BB	–0.21 (–0.34, –0.07)	0.81 (0.71, 0.93)
ACE vs. CCB	–0.22 (–0.44, –0.004)	0.80 (0.65, 0.99)

Table 3: Mixed estimate

Type of estimate	lnOR	SE(lnOR)
Direct	–0.22	0.11
Indirect	0.03	0.13

Thus, the 95% CI for is (–0.23, 0.28). Taking exponential, we get $OR_{ACE\ vs.\ CCB,indirect} = 1.03, 95\%\ CI(0.80, 1.33)$.

Step 3: Compute the mixed estimate for the comparison ACE versus CCB

Create a new data set as shown in Table 3. Perform a fixed effects meta-analysis using inverse variance approach for the data provided in Table 3 to obtain the mixed estimate for the comparison ACE versus CCB.

The mixed estimate for ACE versus CCB in log scale is –0.12 with 95% CI (–0.28, –0.05), which is equivalent to an odds ratio of 0.89 with 95% CI (0.75, 1.05).

Step 4: Check the consistency (agreement between the direct and indirect estimates)

Bucher method is adopted to determine the presence of consistency. This involves computing the IF and testing its significance using Z test.

$$IF = \left|\ln OR_{ACE\ vs.\ CCB,direct} - \ln OR_{ACE\ vs.\ CCB,indirect}\right| = |-0.22 - 0.03| = 0.25.$$

$$Var\ IF = Var\ \ln OR_{ACE\ vs.\ CCB,\ direct} + Var(\ln OR_{ACEvs.CCB,indirect}) = 0.01 + 0.02 = 0.03.$$

$$SE\ IF = \sqrt{Var\ IF} = \sqrt{0.03} = 0.17.$$

The 95% CI is given by (–0.09, 0.58)

Statistical significance of IF, under the null hypothesis of IF = 0, is tested using Z test as

$$Z = \frac{IF}{SE(IF)} \sim N(0,1).$$

$$Z = \frac{0.25}{0.17} = 1.45.$$

The computed value of Z is less than 1.96; thus, we fail to reject the null hypothesis. Alternatively, if 95% CI for IF includes zero, we fail to reject the null hypothesis. Therefore, it can be concluded that there is no statistical evidence for the existence of inconsistency between direct and indirect estimates of the comparison ACE versus CCB. The interpretation of estimates of NMA is not different from that of the pairwise meta-analysis.

Discussion and Conclusion

This article provides a general primer on the conduct of a network meta-analysis. It takes up data from a published source and shows for a small loop how the estimates are to be calculated. In the loop ACE–BB–CCB, three different estimates are computed for the comparison ACE versus CCB: direct, indirect, and mixed. The indirect estimate is obtained as the difference of the direct estimates of comparisons ACE versus BB and CCB versus BB in log scale. Furthermore, the direct and indirect estimates are pooled together to get the mixed estimate. At this stage, it is necessary to check for the existence of consistency, which is achieved by means of IF. It is important to note that, as the mixed estimate includes both direct and indirect sources of information, it accounts for a broader evidence base and can be computed only if the loop is closed.[11] Open loops provide us only with the indirect estimates. The article provides the computational procedure for a simple closed loop. However, in practical situations, we may come across to very complex loops [Figure 1]. Under such situations, the manual calculation becomes very tedious. Therefore, it is advisable to opt for a suitable statistical package (such as R software, STATA, SAS, etc.) to perform NMA.

We hope that this article makes the researchers more aware that the NMA is not mathematically daunting task but inherently simple and a beautiful procedure. In addition, we hope this motivates the researchers to look in the methodological issues surrounding NMA as there are several issues that need to be looking after within it. Because NMA is an important additional tool for researchers wishing to conduct systematic reviews, an important source of guidance and help is the Cochrane Collaborations' Comparing Multiple Interventions Methods Group (CMIMG).

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