007 is best at poker. What is best for VKC?

Principles and opportunities of network meta-analysis in clinical ophthalmology

Ian Fleming's novels about the fictional agent James Bond, codename 007, have become endearing movie classics with an important cultural impact. Agent 007, of the British Secret Service, is an excellent spy, a fearsome assassin, a sharpshooter like no other, and a master of seduction. In the Casino Royale movie released in 2006, it is also revealed that 007 is the Secret Service's best poker player. A high point of the movie is when 007 wins with a straight flush against the villainous LeChiffre.

How can one determine who is the best at playing poker in a large organization such as the British Secret Service? Although one could, theoretically, arrange multiple rounds of poker between all employees to rank individuals with certainty, this is not practically feasible. In practice, a network of comparisons can often be used for a reliable prediction of poker ranking. For example, employee A may have played against employee B, employee B may have played against employee C, and so on. Based on the results of their poker games, there is often a reasonable understanding of who is best.

Instead of 007, consider a hypothetical poker game ranking between the three authors of this paper. Marie Louise wins against Line. Line wins against Yousif. Based on this information alone, we can predict that, in terms of poker, Marie Louise must be the best (followed by Line, and then Yousif). We can put a ranking order even though we have no data on how Marie Louise performs against Yousif (**Figure 1A**). This is possible because we have data on direct comparisons, which we can extrapolate to make indirect comparisons (**Figure 1B**).

Now, consider another hypothetical poker ranking situation between the authors. Marie Louise wins against Line. Line now loses against Yousif. In this scenario, the situation is slightly more complicated, but a ranking order is still possible if we have data on the game results of the individual plays (**Figure 1C**). If we extrapolate this concept of comparisons in a network, we can use this concept in clinical ophthalmology to rank treatments according to their clinical efficacy using the principles of network meta-analysis.

Principles of network meta-analysis

Conventional comparative meta-analyses are made by summarizing the differences between pre- and post-intervention outcomes between two groups, e.g., a treatment group against a placebo group. While such meta-analyses provided a much-needed summary of evidence decades ago, the evidence base today is much larger and more diverse, and more than one or two treatment options exist. Additionally, we now have extensive computing power available at minimal cost.

Multiple treatment comparison meta-analyses allow comparison of three or more groups. Consider a simple case, where a group of studies have compared placebo against treatment A, another group of studies have compared placebo against treatment B, and no studies have compared treatment A to treatment B. A conventional meta-analysis would not be able to provide any insight into how treatment A compares against treatment B. But, if we use multiple treatment comparison meta-analysis, we can compare all groups, even treatment A vs. B in an indirect comparison, given the condition that we can draw a complete network across these groups of interest (**Figure 2**). Therefore, such meta-analyses are more popularly called network meta-analyses. In many circumstances, there is a mix of comparisons, which allows both direct and indirect comparisons as well as their summary estimate. A reference group is defined, upon which the summary estimates of all interventions can be ranked. This reference group can be placebo, but depending on the research question, it may be more appropriate to select an active treatment group as a reference, e.g., a best practice or gold standard to which other treatments can be compared.

Limitations, quality issues, and bias are important to understand when conducting and interpreting such studies. A clear research question, a well-conducted systematic literature search, and a qualitative review are mandatory aspects, just as in any other synthesis of evidence. The study design of overlapping systematic reviews is one of the main reasons why meta-analyses on the same topic can reach different conclusions.[1] For example, should different doses of the same drug be pooled into one category? Can different drugs of the same pharmaceutical category

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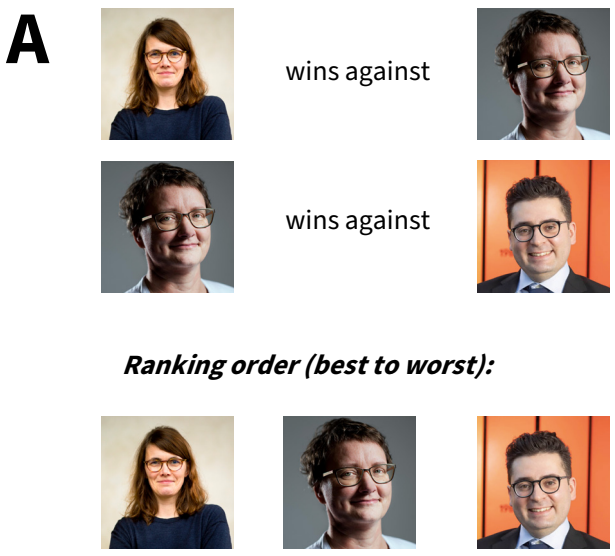

Figure 1. Consider a hypothetical poker game ranking situation between the three authors of this paper. A: Marie Louise wins against Line, and Line wins against Yousif. In this situation, it is intuitively obvious that Marie Louise must be the best, Line the second, and Yousif the worst. B: Although it seems intuitively obvious to rank these three authors, what we actually do in our minds is to use our knowledge of direct comparisons to make indirect comparisons. We can infer the outcome of Marie Louise vs. Yousif even without data on the direct comparison. C: The situation gets more complex if Marie Louise wins against Line, but Line loses against Yousif. Now, we need more data to calculate the ranking order. A network meta-analysis is based on this simple principle. When a network can be drawn between different treatments and data allow calculation, we can use direct and indirect comparisons to calculate summary estimates of efficacies and rank order treatment modalities on outcomes of interest.

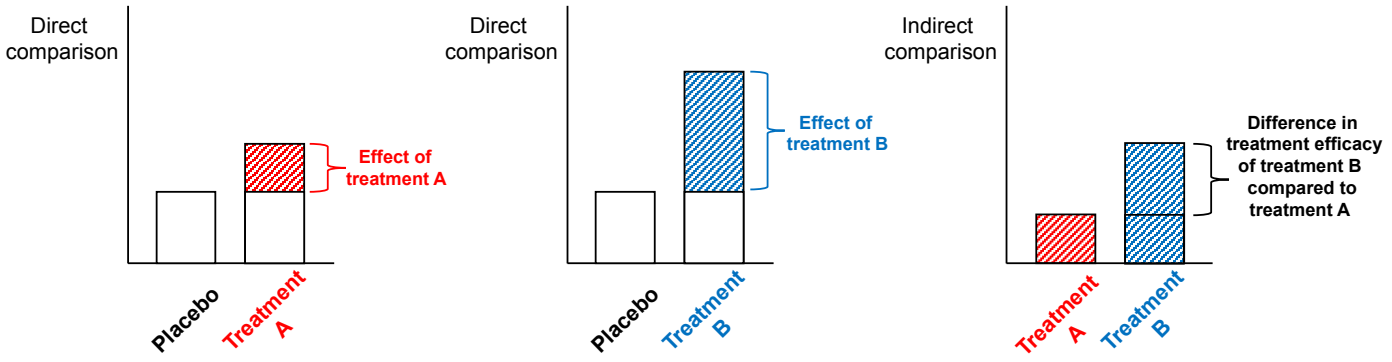

Figure 2. Consider a situation where one group of trials investigated the efficacy of placebo against treatment A (direct comparison) and another group of trials investigated the efficacy of placebo against treatment B (direct comparison), but no trials have compared treatment A and B. Using the outcomes from the direct comparisons*, it is possible to calculate efficacy estimates to perform an* indirect comparison.

be pooled into one category? How about different treatment regimens?

When dealing with network meta-analyses, it is important to keep in mind that the network of direct and indirect comparisons affects the overall summary estimate of a certain treatment and that different approaches to generate the network can lead to different outcomes. For example, consider a case where one systematic literature search excludes outdated treatments while another search includes such treatments. Because of direct and indirect comparisons, the summary estimates of different treatments will differ between the two network meta-analyses. This circumstance favors a more comprehensive literature search and broader eligibility criteria when conducting such network meta-analyses, but it also highlights the necessity of careful consideration of study design when planning such studies.

Another interesting aspect of network meta-analyses is that within the network, there can be groups or areas with specific biases that do not exist in other areas of the network. For example, the presence of publication bias in industry-sponsored trials is well-documented. If the network includes both industry-sponsored and investigator-initiated treatments, then a part of the network may be affected by this publication bias. In a similar fashion, other biases specific to treatments may affect one part of the network but not the other. It is unrealistic to expect to fully control such biases or a situation without any source of bias when conducting network meta-analysis. Therefore, careful consideration and discussion are the cornerstones of every such evidence synthesis, preferably facilitated by tools developed to summarize and ease the interpretation of these biases within and across studies.

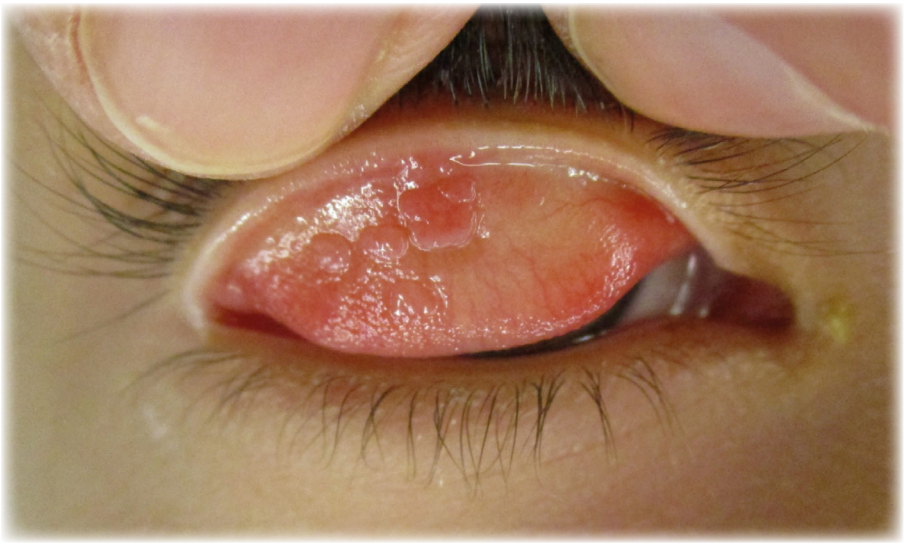

Figure 3. Clinical example of vernal keratoconjunctivitis with hallmark giant papillae located on the upper tarsal conjunctiva, clearly visualized on eversion of the upper lid.

Vernal keratoconjunctivitis: Many comparisons, ideal case

Vernal keratoconjunctivitis (VKC) is a disease of chronic conjunctival inflammation with hallmark giant papillae and Horner-Trantas dots (Figure 3). Although its pathophysiology remains incompletely elucidated, we know that it is in the category of allergic keratoconjunctivitis due to similarities in terms of allergic predisposition, eosinophilic infiltration, and inflammatory milieu. VKC is a relatively rare disease in Nordic countries, with an estimated prevalence of 3.2 per 10,000, and usually presents in pediatric populations.[2]

The overlapping allergic and inflammatory pathophysiology may allow for a range of clinical trials using different treatment modalities. No perfect treatment exists, to the frustration of the patient, parents, and physicians. Interestingly, this is an area where the broad range of treatment modalities have been compared in a fashion that allows a complete network (**Figure 4**); thus, it is a good case for a network meta-analysis to compare clinical efficacy.

Comparative efficacy of medical treatments for VKC across symptoms and signs

We began our work by conducting a state-of-the-art systematic review following PRISMA and the Cochrane Handbook. Our review was based on 39 comparative studies, of which 23 provided data that allowed meta-analyses. We evaluated efficacy as the change in four symptoms (itching, tearing, photophobia, and foreign body sensation) and four signs (hyperemia, punctate keratitis, Horner-Trantas dots, and giant papillae).[3] Effect size was measured by the standardized mean difference and calculated relative to placebo. The analysis of the Horner-Trantas dots is provided as

an example in **Figure 5**. Considering the comparisons available, it becomes clear that conducting conventional pairwise comparative meta-analyses of identified treatments could lead to difficulties in interpretation, counteracting the purpose of providing an overview.

Our study found a general trend of better efficacy using corticosteroids and highlighted that the range of therapies provided different efficacy across signs and symptoms. This is an excellent example of how network meta-analyses can help clinical practice. These rankings provide better certainty in how to interpret and rank existing therapies, which we used to create a national guideline for the treatment of VKC.[4]

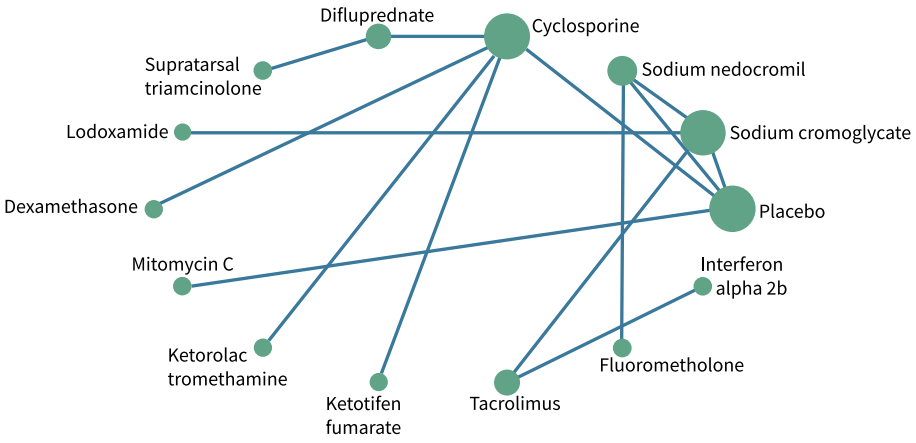

Figure 4. A network plot from a network meta-analysis on the comparative efficacy of medical treatments for vernal keratoconjunctivitis.[3] This network plot is from the analysis of the efficacy on Horner-Trantas dots. The size of the dots indicates the number of studies available with that individual treatment or placebo group. Lines between the dots indicate the existence of at least one study. In this example, a network can be drawn between all studies that evaluate Horner-Trantas dots.

Direct estimates

Active	Control	Cohen's d	LCI 95%	HCI 95%
Sodium cromoglycate	Placebo	-0.71	-1.09	-0.32
Sodium nedocromil	Placebo	-0.68	-1.11	-0.25
Cyclosporine	Placebo	-0.69	-1.60	0.22
Difluprednate	Cyclosporine	-1.14	-4.04	1.77
Difluprednate	Supratarsal triamcinolone	0.00	-3.96	3.96
Lodoxamide	Sodium cromoglycate	-0.38	-1.41	0.64
Dexamethasone	Cyclosporine	-0.18	-0.39	0.02
Mitomycin C	Placebo	-0.99	-1.79	-0.19
Ketorolac tromethamine	Cyclosporine	0.15	-0.94	1.25
Cyclosporine	Ketitofen fumarate	-0.39	-1.07	0.29
Tacrolimus	Sodium cromoglycate	-0.15	-1.30	0.99
Sodium nedocromil	Fluorometholone	0.32	-0.71	1.35
Sodium nedocromil	Sodium cromoglycate	0.07	-0.60	0.74
Tacrolimus	Interferon alpha 2b	0.00	-0.62	0.62

Concluding remarks

The network meta-analysis is a great tool for evidence synthesis and allows for comparison of three or more groups. Clinical ophthalmology can benefit from such analyses, especially considering the incredible amount of clinical evidence published today. However, careful conduct and interpretation are necessary to avoid being misled rather than being guided for better patient care. Ideally, we want to be like 007—careful in handling situations, with an eye for detail, and triumphant in the end.

Summary estimates (direct + indirect estimates) with placebo as the reference in a forest plot

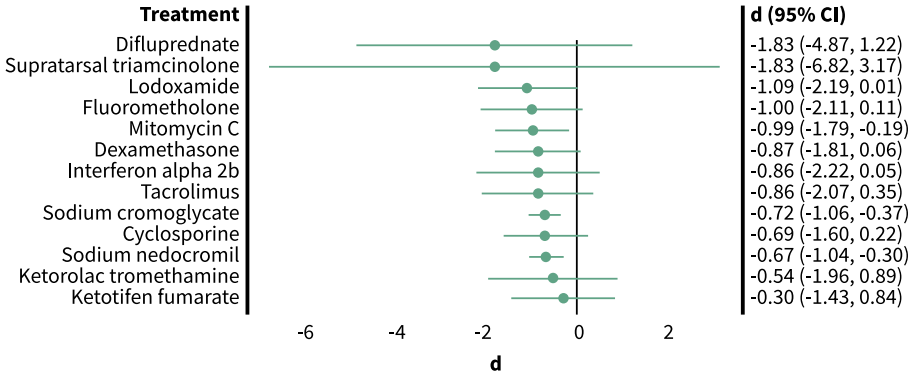

Figure 5. This is an example of the calculations from a network meta-analysis on the comparative efficacy of medical treatments for vernal keratoconjunctivitis, specifically from their analysis of the efficacy on Horner-Trantas dots.[3] Each of the rows in direct estimates are similar to the results that would be obtained from a classical pairwise meta-analysis, e.g., the meta-analysis of all studies comparing sodium cromoglycate vs. placebo lead to a lower degree of Horner-Trantas dots in the group of sodium cromoglycate at a Cohen's d of -0.71 (CI 95%: -1.09 to -0.32). After calculating indirect comparisons, the results are summarized into a final summary estimate, which is, in this case, ranked in order of efficacy and presented in a forest plot.

Key points:

- The large evidence base of modern medicine provides data on a diverse range of treatment options.
- Network meta-analyses enable comparison of 3+ groups between one another and allow ranking of multiple treatment options.
- Methodological limitations and sources of bias necessitate a careful approach to conducting and interpreting such analyses.

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