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***Biostatistician's Eyes** / Biyoistatistikçi Gözünden*

Infective endocarditis after the transcatheter method compared to surgical pulmonary valve replacement: A meta-analysis study- What is meta analysis?

Cerrahi pulmoner kapak replasmanı ile karşılaştırıldığında transkateter yöntemi sonrası enfektif endokardit: Bir meta-analiz çalışması- Meta analizi nedir

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In recent years, the number of scientific studies has been rapidly increasing, and accordingly, different results are often encountered in independent studies on a specific subject. Comprehensive and reliable studies are needed to interpret this body of information and lead to new studies. Meta-analyses, frequently encountered in international scientific medical journals, offer this opportunity by statistically combining the results of multiple studies, and they are considered the highest level of evidence when the results of high-quality randomized trials are suitably combined.[1] In a meta-analysis, which is a quantitative method based on combining the findings obtained from different studies, the data are not combined, and a common result is tried to be reached with the help of statistical inferences. Researchers try to estimate valid and reliable parameters with minimum variance regarding the subject they are investigating. Furthermore, they try to increase the sample size and precision of parameter estimations. This technique can prove useful when there are several similar clinical trials with or without consistent outcomes or when there are smaller to medium-sized trials with inconclusive results.[2]

Appraisal of a meta-analysis includes a critical evaluation of the research question, the literature research, the study selection, the data abstraction, quality assessment of the studies included, and data analysis.[3,4] When evaluating a meta-analysis, it should be reviewed whether the research question is clearly defined and whether the literature study is systematic and reproducible. In addition, the study selection process should be systematic, and the quality assessment of the included studies should be done. When combining the studies, the use of statistical methods and the homogeneity of the studies used should also be taken into account. If there is heterogeneity, it is also valuable to conduct a sensitivity analysis to determine its source. In addition, publication bias should be evaluated, and the suitability of the analysis as a whole should be determined. By combining the results from two or more studies, a meta-analysis can increase statistical power and provide a single numerical value of the overall treatment effect.[5] The meta-analysis result may show either a benefit or lack of benefit of a treatment approach that will be indicated by the effect size (standardized mean differences), which is the term used to describe the treatment effect of an intervention.

A researcher applying meta-analysis explains the relationships between research findings and characteristics by converting the results from different studies into a common measure called effect size. Thus, they find the opportunity to explain the magnitude of

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the relationship between the variables by revealing the deviation level of the sample results from the predictions stated in the null hypothesis. If there is no relationship between the two variables, the effect size is zero. Effect size was first developed by Cohen in 1977, and the most common measure of effect size is "Cohen's d," which is the difference between the experimental group and the control group divided by the standard deviation of one of the two groups. Cohen described the degree of effect as small when d = 0.2, medium when d = 0.5, and large when d = 0.8. The most important reasons why the estimations of effect sizes differ between studies are sample size, variance, and reliability of outcome measures. Moreover, variables such as sex, age, or differences in the intervention provided (e.g., the dose) can influence the magnitude and direction of the effect size. It is necessary to know the effect size of each of the studies included in the analysis. It is possible to benefit from summary statistics for the effect size that does not need raw data in its calculation. For example, if the outcome variable of interest in the research is quantitative, the effect size is determined by the mean, while if the outcome is nominal, it is determined by the ratios. If the outcome variable represents the relationship, the correlation is used to determine this magnitude. When setting up a meta-analysis study, a researcher should consider the basic concepts, such as relative risk, odds ratio, heterogeneity, the model used to conduct the meta-analysis, the forest plot, and the effect size. In meta-analyses, it is essential to define the heterogeneity that shows the variability between studies as heterogeneity has both statistical and clinical significance. Statistical heterogeneity occurs when the treatment effect estimates of a set of studies vary among one another.[6] Since some variation among studies in treatment effect would be expected by chance, statistical heterogeneity refers to the amount of variation in treatment effect present beyond chance.[6] It is possible to evaluate statistical heterogeneity with the help of statistical tests. However, there is no definitive guideline accepted in the literature regarding the inability to complete the meta-analysis due to the presence of statistical heterogeneity; therefore, the appropriateness of the analysis is at the discretion of the researcher. Differences in study methods that affect the ability to compare or combine data from different studies are explained as clinical heterogeneity. The risk or severity of disease, the settings in which the trial is conducted, and the frequency and intensity of the intervention can lead to clinical differences. However, as with statistical heterogeneity, clinical heterogeneity cannot be demonstrated by tests, and its degree cannot be determined. Consequently, researchers decide whether the studies contributing to the analysis are similar enough to make their meta-analysis reasonable. The model selection used to conduct the meta-analysis is a crucial step of the analysis, and the fixed and random effects models, which handle statistical heterogeneity in different ways, are the most commonly used. These models differ from each other in the assumptions about the observed differences in the study results of interest but often yield similar results as long as the heterogeneity is not excessive. In the fixed effects model, it is assumed that all studies participating in the meta-analysis predict the same true effect (a common single and fixed effect). In other words, the population effect size is assumed to be the same in all studies. The most commonly used fixed effect methods can be listed as the inverse variance method, Mantel-Haenszel method, and Peto method. In the random effects model, it is assumed that studies can predict different population effects. That is, the population effect size in all studies is different. The effect size estimated as a result of the meta-analysis is the estimation of the mean of these different effect sizes as there is randomness. Since the variance between studies is taken into account in the random effects model, wider confidence intervals are obtained. Additionally, the heterogeneity of studies can be determined and is more sensitive in small studies. The random effects model has a larger variance than the fixed effects model. The researcher who performs the meta-analysis first calculates the average effect size value with both the fixed effect and random effects model, then creates a forest plot and visually shows how the studies are distributed around the average effect size value. A common effect size calculation method using the random effects model is the Der Simonian and Laird method. The kind of inference made to choose either fixed or random effects models is of great importance. While the fixed-effects model is suitable for inferences only for the studies included in the meta-analysis, the random effects model allows for generalized inferences beyond the studies included in the meta-analysis.[7] Nonetheless, in the fixed effects model, the only source of variance is the estimation of within-study error. Thus, if a large enough sample is provided, the cause of the variance disappears, and the joint effect size can be accurately estimated. There are two causes of variance in the random effects model, within-study error estimation and between-study variance. If a sufficiently large sample is provided, the effect of the first cause of the variance disappears. However, between-study variance is not easily solved. The only way to get better results is to increase the number of studies.

In addition to heterogeneity, model selection, effect size, and forest plots, an important element of meta-analyses, should be considered. Forest plots are often used to show the effect sizes of the studies included in the meta-analysis. The forest plot, as well as showing the effect size and confidence interval of each analyzed study, demonstrates the total effect size and confidence interval of all studies included in the analysis.[8] The size of the black boxes in the forest plot is found by dividing the sample of a study by the size of the entire sample included in the study. The size of the box is also proportional to the information obtained from the relevant study. The length of the horizontal lines running through the middle of the boxes indicates the confidence interval of the relevant study. If these lines are short, the confidence interval is narrow, but the sensitivity is high, and when the lines are long, the confidence interval is wide, but the sensitivity is low. The tile or diamond at the bottom shows the overall effect size. The width of the tile indicates the confidence interval of the effect size, and the height indicates the odds ratio or risk ratio. The line that vertically passes through point 1 (this line is considered 0 when nonlogarithmic values are used) is the no effect line. The ineffectiveness line separates the experimental and control group findings. If the horizontal line showing the confidence interval of any study crosses the ineffectiveness line, this study has no statistical significance. The tile showing the overall effect size should not intersect with the ineffectiveness line for the meta-analysis to be statistically significant. The tile to the left of the ineffectiveness line (on the experimental group side) indicates that there is a significant effect size in the experimental group, that is, the experiment is effective; the one on the right (control group side) indicates that the effect was significant in the control group and the experiment was not effective. A tile that does not cross the ineffectiveness line indicates that the difference between groups is statistically significant.[9] A funnel plot, another type of graph used in meta-analyses, helps to identify possible publication bias. It shows the relationship between the effect size of a study and the study size. If there is no publication bias, this graph resembles an inverted symmetric funnel.[10]

Evaluations regarding the analysis will guide the implementation of the analysis. Rosenthal and DiMatteo[11] summarized the meta-analysis implementation stages. According to Rosenthal and DiMatteo, the dependent and independent variables of the meta-analysis should be determined. All published and unpublished studies on the subject should be systematically obtained. The method and conclusion part of the study should be carefully read. Dependent and independent variables should be determined, and the data should be carefully examined. The variability (heterogeneity) between the obtained data should be analyzed with the help of graphs and tables. Tests (e.g., chi-square) to determine the measure of heterogeneity should be used. Standard deviations that do not depend on sample size can also be used for heterogeneity. Effect sizes should be combined using measures of central tendency such as median and weighted and unweighted means. When examining the significance levels of the effect sizes' central tendency indices, the confidence intervals of the weighted mean for the fixed effects model and the confidence intervals of the unweighted means for the random effects model should be used. The data obtained as a result of the analysis are evaluated. After the completion of these stages, the analysis is reported and concluded.

In this study, meta-analysis was used to evaluate the risk of infective endocarditis in patients with transcatheter pulmonary valve replacement (TPVR) and surgical pulmonary valve replacement (SPVR). Transcatheter pulmonary valve replacement and SPVR are the treatment options for right ventricular outflow tract (RVOT) dysfunction in congenital heart disease patients. PubMed, Cochrane, EMBASE, Scopus, and Web of Science databases were systematically searched for studies reporting 21 infective endocarditis event rates in both TPVR and SPVR, and a random effects model was used for the meta-analysis. The study included 4,706 patients and 15 comparison groups. Patients with TPVR had a higher risk of infective endocarditis than patients with SPVR (odds ratio: 2.68, 95% confidence interval: 1.83 to 3.93, $p<0.00001$). The calculated absolute risk difference was 0.03 (95% confidence interval: 0.01 to 0.05); this means that if 25 surgical valve replacements are performed in 1,000 patients, 30 cases of infective endocarditis will be prevented. The meta-regression of the follow-up period in the incidence of infective endocarditis was not statistically significant ($p=0.753$). According to the results obtained from this study, although TPVR is a feasible alternative to SPVR in severe RVOT dysfunction, the higher incidence of infective endocarditis in TPVR remains a significant concern. Regarding this analysis, it was stated that surgical treatment of RVOT dysfunction is still a viable option in patients with prohibitive risk.

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