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Statistical Errors in Ophthalmic Research

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"Biomedical statistics is essential part of any scientific study; a review of the current scientific literature indicates that statistical analysis is an area that frequently needs improvement. To address this, we put forward some of the most common errors in statistical analysis of ophthalmic data. In ophthalmic data generally when statistical tests are performed, the correlation generally present between observations made for the right and left eyes of a subject, is ignored or is not taken account for. The error leads in a consequence of over statement of the precision of the study that is resulting incorrect P values indicating a greater measure of statistical significance than the data warrant."

Why do we use statistics? It is very essential need of the developing world but in a perfect world specially, with reference of ophthalmology, we would simply conduct experiments and if we obtained differences among the groups, we would conclude that our manipulations caused an effect. However, there exists variability in the world, which is also reflected in our data. Because of this variability, we need the methods of determining which variations in the data are due to the true differences, which are the parts due to variability. It is important to understand the underlying sources of variability. Statistical tools are applied not only to understand the sources of variability but also to measure the extent of experimental error. Our main purpose is to provide a fundamental understanding on how to use these statistical tools appropriately to maximize precision in data interpretation. A more comprehensive review can be found, for instance, in Strasak et al.[9]

The consequences of ignoring the two-eye nature of a design are quite serious in the sense that it provides an over statement of the precision of statistical estimates. This manifests itself in reported measure of variations and standard errors which are too small, confidence intervals which are too sharp and P-values which are incorrectly small. All these measures indicate a greater measure of statistical significance than the data warrant. The reporting of the result which seems to be significant, in fact, loses their significance when the data are correctly analyzed.

There are debates and questions are raised whether the inter-eye correlation should be considered**.** In a typical study, the investigator places the subjects into groups, each of which represents a different experimental treatment or subject factor. The main goal is to assess differences between groups. In a treatment study, the hypothesis tested is that the outcome for treated subjects is superior to that for controls. In an observational study, differences in the natural history of disease between subject groups (e.g., males and females) are assessed. Statistical analysis of the data calculates two quantities, one is the difference in the response measure between the groups and another is the precision of that difference. It is quite often that these two quantities are a mean difference and its standard error. By comparing the magnitude of the observed difference with its precision, the investigator finds the likelihood that an observed difference is the result of chance. Precision of the statistical analysis depends upon two factors: variability of the measurements and the number of subjects. As the number of subjects increases, so does the precision. This principle describes the error in analyses which ignore the positive correlation between the eyes of a subject. In the presence of such correlation, the two eyes of a single subject do not contain as much information as do two eyes, each from a different subject. In the various extreme cases where the correlation is one, it is evident that the second eye of a subject contributes no new information at all. There are many standard statistical tests available where we assume that all observations contain the same amount of information, that they are uncorrelated. The specialized case of ophthalmic research requires statistical methods which takes into account the potential inter-eye correlations.

Placement of eyes into experimental groups, how eyes are placed into experimental groups is a crucial aspect of research design that profoundly influences subsequent statistical analysis. Nearly all ophthalmic investigations fall into one of three categories: one-eye designs, two-eye designs, or paired eye designs.

In a one-eye design, only one eye of each subject is part of the study. Such designs are often required by humane treatment considerations. In paired-eye designs reduce variability in response due to subject heterogeneity by using subjects as their own controls. For a given subject, each eye is treated differently. These designs are ideal for the measurement of the efficacy of a single treatment: one eye is treated and the other eye serves as control. Paired-eye designs are valid when the effects of treatment remain localized within a single eye. In this case, such designs can increase experimental precision substantially.[1] While two-eye design, the most frequently employed in ophthalmic research, each subject is assigned to a group. For each subject, both eyes are in the same group. As a consequence, the subject contributes two measures of response, which are positively correlated in most ophthalmic studies.[4]

In Analysis of the one-eye design, only one eye from each subject is part of the experiment, analysis of one-eye designs can use familiar statistical techniques: chi-square analysis for binary variables, and t-test or analysis of variance for continuous variables. In analysis of the paired-eye design, the paired t-test is the appropriate technique for the most frequent form of this design, in which one eye of each subject is treated and the other eye serves as a control. Analysis for generalizations of the paired-eye design that allow more than two groups, called balanced incomplete block designs, requires specialized analysis of variance techniques.[2] Where as in analysis of the two-eye design must take into account the fact that each subject contributes two observations. If the outcome measures are continuous,[7] two approaches are acceptable. The first is to average the single-eye observations for each subject and then to perform one of the analyses described for one-eye designs on the averages. This approach adequately tests for differences between treatments. It is the simplest approach, particularly when certain subjects have data missing from one of the eyes. However, more complex statistical analyses can provide additional information about sources of variability. These analyses partition variance of the outcome measure into two components: that resulting from differences between subjects, and that resulting from differences between eyes, within subjects.[8,6] If there are two observations for every subject, these components of variance can be estimated with a nested analysis of variance[4,8,3] (often termed analysis of variance with sub sampling). If data from some of the eyes are missing, specialized components of variance analyses[5] can be performed. For binary responses, Rosner has described appropriate statistical methods.[4]

When lack of inter-eye correlation could be assumed? In principle, the choice of statistical analysis may be based upon the observed inter-eye correlation. This approach requires estimating the inter-eye correlation and testing the hypothesis that it is zero. It is permissible only when,[1] there is strong biological plausibility that the correlation between the eyes of a subject is zero; and[4] there is statistical evidence that this correlation is zero. Sample size should be adequate to guard against a false negative, or Type II statistical error. In practice, we strongly recommend routine use of two-eye analyses. Experience has shown that for ophthalmic data, right and left-eye observations usually have high positive correlation.[1,4] It is because subject characteristics are manifested in both right and left-eye measurements. Furthermore, there is little penalty for use of two-eye analysis, even when the inter-eye correlation is zero. In this circumstance, a two-eye analysis will produce a slightly conservative estimate of precision.[3]

Statistics provide tools that allow us to make inferences about our data. Every statistic is based on a series of assumptions about how the data set is being used to evaluate. If these assumptions are violated, then the statistic is no longer a valid measure of the variability for which we are using it to assess, it becomes invalid. Therefore, it is important that investigators take care with their data analysis that they take setting up their research protocols and obtaining their data. Statistics can greatly enhance our ability to learn from our results but when not done carefully it can also lead to misinterpretation.

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