Evidence-biased medicine: Intention-to-treat analysis less conservative?
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Abstract
Evidence-based epidemiology requires a rigorous but creative analysis of data. Intention to treat (ITT) analysis (i.e. taking into account the last data available for any subject included and for whom a point baseline evaluation is available) is commonly accepted as more conservative than the per-protocol (PP), restricted to the analysis of the data of subjects who completed the study. Commonly, the within-groups differences being smaller in ITT than in PP, their statistical comparison lead to a smaller risk of type I error (i.e. inappropriately concluding to a difference while there is not). It also allows for keeping the randomization scheme (i.e. the balanced distribution of confounding factors), and thus not leading to a differential distribution of confounding factors between groups if more subjects are withdrawn from the study in a given group.

However, there is a particular condition in which ITT is less conservative, and thus leads to a higher risk of concluding to a difference in absence of real one. The table below displays the results of a hypothetical trial. The mean values and their standard deviations for group I and group II, before and after intervention are shown. The treatment allocated in group I induces a smaller effect in limiting the decrease of the outcome than the treatment received in group II. In patients finishing the trial, we assume a 20 (34)% reduction in group I and a 30 (27)% in group II. The losses to follow-up values are considered normally distributed between “before” and “after” values. The loss to follow-up in Group I is 50% while 10% in Group II.

If we compare the changes between group I and II in PP and ITT using a classical unpaired Student t-test, we obtain $p=0.06$ (NS) and $p=0.008$ (S), respectively.

The higher loss to follow-up rate in group I made the delta smaller in ITT (more subjects left the trial before the benefits of the whole effect of the treatment). In group II, that rate being much smaller, the delta did not vary much, since only 10% of the subjects had an intermediate value between “before” and “after”. The resulting global difference of the variations observed within groups was therefore higher in ITT and the $p$-value smaller.

In a clinical perspective, such a situation can be encountered when the investigational treatment aims at preventing the decrease of the main outcome e.g. a symptomatic effect. If the onset of action of the experimental drug is longer than for the comparator, notwithstanding its superior efficacy at the trial end, the probability that more patients quit the “treatment” arm than the “control” one is high. Since the mean effect observed for loss to follow-up patients is below the one of per-protocol ones (they quit the trial very early), the mean difference in ITT will be superior than the one observed in per protocol. Once in a blue moon...

References