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Letter to the Editor

Caution Should Be Observed Against the Last Observation Carried Forward Analysis in Opioid Trials

Opioid Çalışmalarında İleri Taşınmış Son Gözlem Analizine Karşı Temkinli Olunmalıdır

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Randomized placebo-controlled trials are considered to be essential because they are expected to provide unbiased results. However, numerous problems have been reported to be associated with systematic biases.[1] Among these biases, the attrition bias is somewhat different in that it cannot be controlled solely by the effort of researchers. This type of bias was emphasized by a previous study finding in which many participants with knee osteoarthritis (OA) dropped out of the trials due to complaints of ineffectiveness and adverse events.[2] Because attrition bias is inherently related to the participants themselves, researchers have developed indirect methods whereby it can be prevented.

The intention-to-treat (ITT) analysis has been employed as a safeguard from such bias. However, handling missing data is another problem in statistical analysis. Specifically, it has been argued that the last observation carried forward (LOCF) method is inappropriate because it assumes that the participants' condition is stable at the value observed before dropout.[3] As Molnar et al.[3] reported, when more dropouts occur in the treatment group than the placebo group, the LOCF approach causes a bias in the results in favor of the test treatment.[3] In fact, the bias caused by the LOCF approach has been demonstrated in simulation studies using knee OA data[4] and rheumatoid arthritis (RA) and osteoarthritis (OA) data.[5]

To confirm this possibility in "real" knee OA data, we searched the MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases for randomized, placebo-controlled trials that had been published through December 2011, and extracted data from 294 studies, that including dropouts in the treatment and placebo groups. The pooled dropout rate, based on a random effects model, was 14.7% [95% confidence interval (CI): 13.6-15.9]. When the relative risks categorized by treatments were calculated, there were more dropouts in the treatment group for opioids (1.22; 95% CI: 1.07 to 1.38) and matrix metalloproteinase (MMP) inhibitors (2.45; 95% CI: 1.40 to 4.29). For the opioids, 10 of the 11 trials used the ITT analysis six utilized the LOCF approach, but the other trials did not specify any approach. For the MMP inhibitor trials, the ITT analysis was not used.

Considering the high prevalence of conditions promoting the LOCF analytic bias, it is very likely that the results of the opioid trials may have been affected in a multitude of ways. Although the magnitude of such

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bias needs be demonstrated in future studies, this finding is meaningful in clinical practice. Because the results in favor of toxic treatments may be exaggerated by this bias, less toxic treatment options may not be prescribed.[3] Therefore, physicians may not be able to satisfy the needs of their patients regarding the management of painful knee OA. To accurately estimate the magnitude of treatment efficacy, caution should be observed regarding the LOCF analytical bias. In this respect, the study by Erdogan et al.[5] is to be congratulated.

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