Editorial

Can We Trust Knee Meniscus Studies? One-Way Crossover Confounds Intent-to-Treat Statistical Methods

Abstract: Randomized controlled studies have a high level of evidence. However, some patients are not treated in the manner to which they were randomized and actually switch to the alternative treatment (crossover). In such cases, "intent-to-treat" statistical methods require that such a switch be ignored, resulting in bias. Thus, the study conclusions could be wrong. This bias is a common problem in the knee meniscus literature.

Randomized controlled trials have a high level of evidence because if patients are randomly assigned to a treatment group (usually one of 2), random assignment minimizes differences between groups, reducing bias. Unfortunately, patients may be noncompliant with their assigned treatment and even switch or "cross over" to the other treatment being studied. For example, if a study subject is assigned to take aspirin and if that subject is noncompliant and does not take aspirin, the statistician will paradoxically tabulate the noncompliant subject as if he actually did comply with taking aspirin. Or, if a subject is assigned nonoperative treatment and if that subject is noncompliant and does have an operation, the statistician will paradoxically tabulate the noncompliant subject as if he did not have the surgery.

Intent-to-Treat (ITT) Analysis

The statistical method of ITT ignores patient noncompliance with the original assignment, which has the advantage of replicating noncompliance that actually occurs in clinical practice independent of research. Unfortunately, when it comes to ITT analysis of invasive procedures, the statistical methods seem incorrect because of "1-way" crossover.

One-Way Versus 2-Way Crossover

Two-way crossover, wherein noncompliant patients can switch from one group to another and vice versa, seems problematic—but in actuality, vice versa means the switch can go either way, which minimizes bias. On the other hand, 1-way crossover means that subjects can cross from one group to the other, but not vice versa. This actually introduces bias because 1-way crossover results in a "marked degree of nonadherence to randomized treatment. This factor reduce(s) the power of the intention-to-treat analysis… (and does) not share the strong protection from confounding that exists for the intention-to-treat analyses."[1]

One-Way Crossover in Surgical Trials

One-way crossover is biased and confounds ITT analyses, resulting in conclusions that may be wrong. Studies comparing interventional (e.g., surgical) versus noninterventional treatment using ITT are biased, because studies comparing surgical versus noninterventional treatments allow 1-way crossover ipso facto; obviously, patients who fail nonsurgical management can cross over and have surgery, but once a patient has surgery, they cannot go back in time and undergo nonoperative management.

"Useless" Surgery

In a column titled "The Upshot," published on August 3, 2016, in *The New York Times*, Gina Kolata wrote of surgery for a torn meniscus cartilage in the knee under the title, "Why 'Useless' Surgery is Still Popular."[2] In the article, Kolata cited "Surgery versus Physical Therapy for a Meniscal Tear and Osteoarthritis," an article published in the *New England Journal of Medicine* in 2013.[3] The conclusions of the 3-year-old article read, "In the intention-to-treat analysis, we did not find significant differences between the study groups in functional improvement 6 months after randomization; however, 30% of the patients who were assigned to physical therapy alone underwent surgery within 6 months."

Later in the current issue of *Arthroscopy*, Arthroscopy Association of North America Second Vice President Louis McIntyre, M.D., advocates,[4] as ever,[5-8] that

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Arthroscopy readers are obligated "to educate patients, and interpreting this type of information is an increasingly demanding but essential task." We fully agree and encourage readers to read and study Dr. McIntyre's expert opinion in the article titled "Making Sure the Media Gets It Right on Orthopedic Research."[4] In addition, from a statistical standpoint, we have concerns that the media "got it wrong."

Statistical Analysis of ITT Trials Require Cautious Analysis Because of Crossover

In a randomized clinical trial where the 2 potential treatments are surgery or physical therapy, patients are randomized to receive one of the 2 treatments. This randomization should "balance" all background patient characteristics that exist before treatment. Thus, when the 2 groups of patients are compared on a primary outcome measure taken after the treatment is initiated (i.e., functional improvement 6 months after randomization), one can assume that any difference seen between the groups is due to treatment.

Unfortunately, in many studies, patients may be missing the primary outcome measure because they drop out of the study. If analyses included only patients with the primary outcome measure available, this could undermine the randomization process and lead to potentially biased estimates of the treatment effect, because the group of patients who have the primary outcome measure available may not be a random sample of patients, and the assumption that randomization "balanced" all background characteristics may be violated.

To confront this problem, investigators have often used ITT. This approach requires that all patients who are randomized be included in the final analysis. Although this approach is well accepted in the statistical and medical literature, it is often assumed that patients received the treatment assigned to them. Interpreting the results of a randomized clinical trial can be challenging when a substantial proportion of patients do not receive the treatment that they are randomized to receive.

This challenge becomes more problematic when patients cross over and not only do not receive the treatment they were assigned but in fact receive the treatment they were *not* assigned. If the percentage of patients for whom this occurred is not equal in both treatment groups (i.e., more patients randomized to receive physical therapy actually receive surgery than vice versa), then the interpretation of the actual treatment effect is compromised.

This situation is often confronted in oncology studies, as patients in a randomized trial are often given the option to cross over to active treatment if they experience disease progression during the standard of care treatment. When this occurs, evaluation of overall survival becomes difficult; once a patient crosses over to the active treatment, his or her survival time may be increased. In such studies, progression-free survival (time until the cancer progresses based on a quantitative assessment of the size of the tumor) often is compared between groups because patients would not have crossed over until after the tumor size increased. For overall survival, several analyses are often presented: one that shows the original randomization groups and a second that shows survival times only for patients who did not cross over. (It is usually believed that the actual survival time estimate is a value in between these 2 estimates.)

The point is that in such analyses, it is often understood by researchers that comparison of overall survival between groups may need to be examined with some caution because of the issue of crossover. Other clinicians—such as orthopedic surgeons—may not be as familiar with the potential bias that can occur without a nuanced analysis that accounts for the impact of missing data or possible crossovers.

In the article "Surgery Versus Physical Therapy for a Meniscal Tear and Osteoarthritis" from the *New England Journal of Medicine*,[3] we see a situation where an ITT analysis was performed that may, in fact, have distorted the actual findings of the study. In this particular article, there were at least 2 specific issues that influenced the final results of the article.

The first issue was that the authors only used patients with complete data in their primary outcome analysis. As stated above, when patients with missing outcome data are systematically removed from an analysis, the process of randomization cannot be guaranteed to create balance between groups. The exclusion of patients with missing data implies that the authors did not actually perform a standard ITT analysis.

The second issue was that 30% of the patients assigned to undergo physical therapy had actually undergone surgery by the time of the primary outcome measure, whereas 9% of the patients assigned to surgery had not undergone surgery at 6 months. This situation could introduce bias because 30% of patients in the Physical Therapy group could receive a larger improvement in their Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score because they received the surgical treatment. Likewise, 9% of the surgery patients could have received a smaller improvement in their WOMAC scores because they received no intervention. (Not receiving surgery does not indicate receiving physical therapy in this situation.) We now examine these potential biases.

Potential Biases Mandate Nuanced Reconsideration

The authors of "Surgery Versus Physical Therapy for a Meniscal Tear and Osteoarthritis"[3] showed that