A systematic review of the sensitivity of efficacy endpoints TOTPAR and SPIID in acute pain

Poster #142, American Pain Society Meeting, New Orleans, LA

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Introduction

Acute analgesic clinical trials rely on two different efficacy paradigms, pain intensity and pain relief, to assess treatment effect. It is currently unclear which efficacy paradigm is more sensitive. This lack of evidence gives rise to a frustrating debate when considering which primary endpoint to choose for an acute analgesic investigation (pain intensity via the use of summed pain intensity difference (SPIID) or pain relief, via the use of total pain relief (TOTPAR)). Ultimately, the decision is generally haphazard and usually made based on expert opinion. Because many investigations utilize multiple endpoints simultaneously, it was possible for us to retrospectively examine which efficacy paradigm, pain relief or pain intensity, within a single investigation is the more sensitive method to detect treatment effect. Since pain relief is most commonly measured by TOTPAR, and pain intensity by SPIID, we decided that a comparison of the effect sizes of these two measurement outcomes would be more informative for the research community.

Methods

• A systematic electronic search of Medline and the Cochrane Library database was performed to identify double-blind, randomized clinical trials for treatment of acute postoperative pain from 1998-present.

• The key inclusion criteria was that an acute analgesic investigation measured both TOTPAR and SPIID at a single time point. Of the studies that were ultimately identified, each was examined to determine whether TOTPAR or SPIID was the more sensitive assay at the pre-identified single time point within the study that both measures were utilized. The sensitivity was determined by calculating the effect sizes (ES) for both TOTPAR and SPIID. The results were compared as weighted means and analyzed with the R statistical software.

• Whichever endpoint, TOTPAR or SPIID, resulted in a larger ES for the pre-specified single time point within each study was considered the more sensitive assay. From the studies analyzed, we tallied the number of studies whose ES for TOTPAR was greater than SPIID.

Results

• 202 articles were initially found through our search strategy; 35 studies met the inclusion/exclusion criteria and were included in the review.

• The effect sizes from 25 of the 35 (71%) clinical trials assessed revealed that TOTPAR was the more sensitive assay in regards to pain efficacy endpoint.

• The magnitude of the differences between TOTPAR and SPIID ranged as much as 112% more when using TOTPAR as the efficacy outcome.

• Using the sign test, the probability of obtaining 25 of 35 studies demonstrating TOTPAR to be the more robust assay is calculated to be 0.0035, suggesting the study outcomes favoring TOTPAR was more than what would be expected by chance.

Conclusion

• Acute analgesic clinical trials typically rely on two different efficacy paradigms, pain intensity and pain relief, to assess treatment effect. However, it has never been clear which efficacy paradigm is more sensitive.

• Results from our analysis suggest that the pain relief endpoint, TOTPAR, is more sensitive than SPIID as the analgesic efficacy endpoint in single-dose studies of acute postoperative pain.

• Our data underscores the importance of choosing the proper primary endpoint in the design and planning of clinical trials.

• By analyzing methodological issues in analogous clinical trials, we may begin to minimize false negative trials, make smarter trial design choices, ultimately making our clinical trials more cost-effective while decreasing scientific burden.