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Critical Review

Assay Sensitivity of Pain Intensity Versus Pain Relief in Acute Pain Clinical Trials: ACTTION Systematic Review and Meta-Analysis

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Abstract: The magnitude of the effect size of an analgesic intervention can be influenced by several factors, including research design. A key design component is the choice of the primary endpoint. The purpose of this meta-analysis was to compare the assay sensitivity of 2 efficacy paradigms: pain intensity (calculated using summed pain intensity difference [SPID]) and pain relief (calculated using total pain relief [TOTPAR]). A systematic review of the literature was performed to identify acute pain studies that calculated both SPIDs and TOTPARs within the same study. Studies were included in this review if they were randomized, double-blind, placebo-controlled investigations involving medications for post-surgical acute pain and if enough data were provided to calculate TOTPAR and SPID standardized effect sizes. Based on a meta-analysis of 45 studies, the mean standardized effect size for TOTPAR (1.13) was .11 higher than that for SPID (1.02; *P* = .01). Mixed-effects meta-regression analyses found no significant associations between the TOTPAR – SPID difference in standardized effect size and trial design characteristics. Results from this review suggest that for acute pain studies, utilizing TOTPAR to assess pain relief may be more sensitive to treatment effects than utilizing SPID to assess pain intensity.

***Perspective:** The results of this meta-analysis suggest that TOTPAR may be more sensitive to treatment effects than SPIDs are in analgesic trials examining acute pain. We found that standardized effect sizes were higher for TOTPAR compared to SPIDs.*

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***Key words:** Acute pain, postoperative pain, pain intensity, pain relief, summed pain intensity difference, total pain relief, methodology.*

Over the past 20 years, many of the drugs that have progressed to late-phase development have been reformulations of opioids or other molecules with known analgesic efficacy.[32,36] Since the mid-1990s, however, there has been a significant rise in the percentage of negative analgesic clinical investigations.[16,17,35,64,65] If one assumes that reformulated drugs should generally demonstrate efficacy in phase 3, then why should so many late-phase analgesic investigations have negative results? The precise answer is a matter of ongoing debate, but it is clear that in order for any analgesic investigation to yield a statistically significant treatment benefit, it must 1) test an efficacious product, 2) be properly designed, and 3) be conducted with minimal experimental error.

Acute pain analgesic clinical trials traditionally use 2 different efficacy paradigms, pain intensity and pain relief, to assess treatment effect. The results of a systematic review of acute pain clinical trial methods concluded

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that summed pain intensity difference (SPID) and total pain relief (TOTPAR) scores[74] were comparable in their ability to detect analgesic treatment effects.[4] However, this study examined only trials of single doses of aspirin, paracetamol, and ibuprofen, and there were only 3 trials for which SPID and TOTPAR could be compared. It is, therefore, currently unclear whether these approaches to assessing efficacy in acute pain trials are generally comparable or whether one of them has greater assay sensitivity to detect treatment effects. For this reason, decisions about the use of these measures are generally made based on expert opinion rather than on empirical evidence (data).

Because of this uncertainty, many acute pain clinical trials utilize both TOTPAR and SPID. The availability of multiple studies that assessed pain outcomes utilizing different paradigms (TOTPAR and SPID) at the same time provides an opportunity to examine which paradigm (pain relief or pain intensity) is more sensitive to treatment effects.

Methods

Data Sources

A systematic electronic search of MEDLINE and the Cochrane Library database was performed by the first and third authors (N.S. and P.D.C.) to identify randomized, double-blind, placebo-controlled clinical trials of analgesics for treatment of acute postoperative pain. The detailed search strategy included the following subject headings and MeSH terms: "acute pain," "randomized," "placebo controlled," "postoperative," "analgesics in adults." The resulting list was intersected with the following group of terms: "pain intensity," "pain assessment," "SPID," "pain relief," and "TOTPAR." Reference lists, meta-analyses, U.S. Food and Drug Administration summary basis of approvals, and clinical trial register databases, including ClinicalTrials.gov, of relevant studies were also manually screened for quantitative data. Titles and abstracts ranging from January 1999 to September 2013 were independently reviewed by the first and third authors (N.S. and P.D.C.) to determine whether each trial met eligibility criteria.

Inclusion and Exclusion Criteria

For inclusion, trials had to be randomized and double-blind with a placebo control group; include participants who suffered from acute postoperative pain of moderate to severe intensity; and measure both pain relief and pain intensity, assessed by TOTPAR and SPID, respectively, at the same time point. The pain measurement scales accepted for the calculation of TOTPAR were an ordinal pain relief scale (eg, none = 0, slight = 1, moderate = 2, good or a lot = 3, and complete = 4) or a continuous visual analog scale with the ends labeled as "no relief" and "complete relief" and no intermediate divisions or descriptive terms. For SPID, the accepted scales were an ordinal pain intensity scale such as the numerical rating scale (eg, 0 = no pain; 10 = worst pain imaginable) or a visual analog scale with the ends labeled "no pain" and "worst pain imaginable" and no intermediate divisions or descriptive terms. In almost all of the studies, the TOTPAR and SPID data used for our calculations were the prespecified primary or co-primary endpoints. In all cases, the TOTPAR and SPID data used to calculate standard effect sizes (SESs) were from time points after the first administration of study treatment but before the second administration (if multiple doses of study treatment were administered). Publications had to be written in English, subjects had to be 16 years of age or older, and each treatment group in the study had to include at least 10 subjects. Studies were excluded if insufficient information was presented to calculate effect sizes, that is, studies that provided only group means without providing standard deviations or quantities from which standard deviations could be derived (eg, confidence intervals or t-statistics). Other studies that were excluded were those that used active comparators as controls instead of placebos, those that used devices to treat pain, and those that did not examine postoperative acute pain. Even though we did not include the outcome of the trial as an inclusion criterion, our criteria resulted in a pool of articles that did not include any negative trials, possibly because of a bias toward publishing positive clinical trials in medical research.[15,18,25,33,66,67]

Data Synthesis

Data from the original reports were extracted by the second and third authors (M.H. and P.D.C.), and the following information was coded: number of patients per treatment arm, means and standard deviations for SPID and TOTPAR in each study arm, total number of randomized patients in the trial, surgical procedure, methods of pain measurement, trial sponsor, drug type, number of doses, and time from randomization until the endpoint was measured.

Quantitative data from trials where TOTPAR and SPID data were collected at the same time points were used to calculate SESs. When there were multiple treatment groups with varying dose levels, we chose the treatment group with the highest dose. The SESs were defined as the ratio of the treatment effect (mean value in treatment group minus mean value in control group) to the pooled standard deviation of the outcome variable. For each study, a single time point after the administration of the first dose of study medication, but before the second dose of study medication, was selected. The earliest time point that contained both SPID and TOTPAR data was used. An SES was calculated at that time point for both SPID and TOTPAR.

For trials that met all eligibility criteria but did not include standard deviations for the treatment and control groups (n = 4), standard deviations were calculated based on other information provided in the trial. In 3 trials, standard deviations were calculated for the treatment and control groups based on the standard errors reported for each group. For 1 trial, the pooled standard deviation was calculated based on the reported *P* value from an independent samples t-test along with the group means and group sample sizes.

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