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# Analyzing acute procedural pain in clinical trials

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ABSTRACT

Because acute procedural pain tends to increase with procedure time, assessments of pain management strategies must take that time relationship into account. Statistical time-course analyses are, however, complex and require large patient numbers to detect differences. The current study evaluated the abilities of various single and simple composite measures such as averaged pain or individual patient pain slopes to detect treatment effects. Secondary analyses were performed with the data from 3 prospective randomized clinical trials that assessed the effect of a self-hypnotic relaxation intervention on procedural pain, measured every 10–15 minutes during vascular/renal interventions, breast biopsies, and tumor embolizations. Single point-in-time and maximal pain comparisons were poor in detecting treatment effects. Linear data sets of individual patient slopes yielded the same qualitative results as the more complex repeated measures analyses, allowing the use of standard statistical approaches (eg, Kruskal-Wallis), and promising analyses of smaller subgroups, which otherwise would be underpowered. With nonlinear data, a simple averaged score was highly sensitive in detecting differences. Use of these 2 workable and relatively simple approaches may be a first step towards facilitating the development of data sets that could enable meta-analyses of data from acute pain trials.



## 1. Introduction

Contemporary health care strives to be evidence-based. While one properly designed prospective randomized trial may suffice to establish some confidence in the relative risks and benefits of a specific treatment, the highest level of evidence derives from concurrent results of several such trials [3]. The premise of this view is that the measures used in different trials are comparable and can easily be combined and entered in meta-analyses. With objective single-point outcome measures such as disease-free intervals or survival time, the task is relatively straightforward. However, when outcome measures are multidimensional, subjective, and have uncertain trajectories and time intervals across subjects—such as is the case for measures used in pain clinical trials—assessment methods become more complex [7].

The National Institute of Health initiated the Toolbox project to provide a set of brief, validated outcome measures that can be used across diverse study designs. To assess pain, the Toolbox includes a 0–10 numeric intensity rating scale and a pain interference item bank [5]. Investigators still need to decide whether to choose single, multiple, averaged, or otherwise aggregated measures to reflect treatment effects [8].

Common approaches are point-in-time comparisons, the use of averages [1,9,18,19], and maximal pain measures [14,15,17]. Jensen and colleagues showed that in the assessment of chronic pain a single 24-hour recall rating can potentially be as valid (sensitive) for detecting treatment differences as 9 individual measures combined, allowing considerable savings in cost and burden of clinical trials [7] (but see also Stone et al. [16]). Assessing the effect of interventions on stimulus-evoked or procedural acute pain may not, however, be as straightforward, because the time factor is a more critical element of analysis.

In a clinical trial of patients undergoing invasive vascular and renal procedures, patients' pain perception increased linearly over time under standard care conditions [10]. This phenomenon was replicated in 2 subsequent studies [11,12], indicating a need for time-sensitive methods of analysis. However, time-series analyses require large sample sizes and complex statistical approaches. Moreover, with effective interventions, the appearance of zero-score pain assessments can make transformation into normally

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distributed data impossible (as occurred in 2 of the trials cited earlier). This factor makes statistical approaches even more demanding, exceeding the repertoire of many investigators and preventing the inclusion of results in meta-analyses.

The purpose of this study was to evaluate the ability of various analytical approaches to detect treatment effects on acute pain. Examining data from 3 previously published trials, we were particularly interested in whether a single composite pain rating or a relatively straightforward measure, such as slope derived from a per-subject regression analysis, would be as valid as more complex approaches. Because such comparisons, to our knowledge, have not yet been performed, we did not have specific a priori hypotheses regarding which method would be superior. Nevertheless, in the event that one specific data treatment proved to be more valid, there could be significant implications for the design and analysis of acute pain clinical trials.

## 2. Materials and methods

### 2.1. Data sets

We performed secondary analyses using the raw data sets of 3 original prospective randomized clinical trials that had been performed with institutional review board approval and Health Insurance Portability and Accountability Act compliance [10–12].

The trials compared measures of acute pain intensity and anxiety in patients undergoing invasive medical procedures. Patients were randomized to standard care, empathic attention control, or self-hypnotic relaxation groups. The 3 trials differed in terms of access to sedation and invasiveness of the procedures, as well as procedure risk and meaning for the patients. In the "vascular/renal trial" 241 patients undergoing procedures to their blood vessels or kidneys had access to intravenous midazolam and fentanyl through a patient-controlled analgesia model, and had their puncture sites over the groin vessels or over the kidney anesthetized with lidocaine [10]. The "breast biopsy trial" only allowed local anesthetic for biopsies with 8- or 14-gauge devices in a pure outpatient setting with 236 patients [11]. The "tumor embolization trial" was a model of particular invasiveness and enrolled 201 patients with liver cancer or benign uterine fibroids. Patients had access to intravenous midazolam and fentanyl through a patient-controlled analgesia model, had local anesthesia, and received intra-arterial infusion of particles (with or without chemotherapy) to promote organ ischemia, which was expected to set in during the time of treatment with the associated potential discomfort [12].

In the standard care patient condition, personnel were instructed to abstain from suggesting or inducing imagery in the patients, but to otherwise behave naturally. In both the empathy and hypnosis conditions a research assistant displayed a set of standardized behaviors such as adapting to the patient's preferred mode of verbal and nonverbal communication, avoidance of negative suggestions, attentive listening, and providing encouragement, but avoided praise and supporting the perception of control. In the hypnosis condition the research assistant also read a script that included a hypnotic induction followed by generic prophylactic suggestions for pain management.

Features of the primary trials and analyses used in the original trials are summarized in Table 1.

**Table 1**
Features and statistical analyses of the primary trials.

| Trial | Procedure specifics | Mean procedure time | Problems preventing choice of intended analysis | Methods used for published analyses | Results of published primary analyses |
|---|---|---|---|---|---|
| Vascular/renal trial [10] n = 241 | Intravenous sedation | 78 min S<br>67 min E<br>61 min H<br>($P$ = 0.0016) | None; logarithmic transformation allowed normalization of data | Repeated measures analysis with results presented in terms of time trends of pain ratings; linear mixed models estimated by restricted maximum likelihood in BMDP version 5 software {Dixon, 1992 #274} to obtain unbiased estimates of intercepts and slopes; comparison of slopes by two-tailed Wald statistics | Positive linear time trends for S (slope 0·09 in pain score/15 min, $P$ < 0.0001) and E (slope 0.04/15 min, $P$ = 0.0425); slight negative slope for H not different from zero (slope = −0.03, $P$ = 0.234). Trend in H significantly less than trend in S ($P$ < 0.0001) and E ($P$ = 0.0259) |
| Breast biopsy trial [11] n = 236 | Higher anxiety levels than other groups [6] | 46 min S<br>43 min E<br>39 min H<br>($P$ = 0.18) | 47% of pain scores were 0, making normalization impossible and thus not permitting repeated measures analysis | Ordinal regression with results presented in terms of the slopes of the time course of pain on logit scales; data adaptation to assure meeting of the proportional odds assumption of ordinal regression (sparseness of data in the highest response ratings of 8, 9, and 10 requiring collapsing these into a single category) | Significant increase in pain over time in all 3 groups (S slope = 0.53, $P$ < 0.001; E slope = 0.37, $P$ < 0.001; H slope = 0.34, $P$ < 0.001). Increase of slope E < slope S ($P$ = 0.024); slope H < S ($P$ = 0.018), no difference in slopes of E and H ($P$ = 0.73) |
| Tumor embolization trial [12] n = 201 | Intravenous sedation; end-organ ischemia in later part of procedure; concurrent intra-arterial chemotherapy for 88 patients | 110 min S<br>120 min E<br>110 min<br>($P$ = 0.77) | High adverse event rate in empathy group resulted in halting the trial with fewer than planned 350 patients; bimodal distribution of pain ratings (Fig. 1) did not allow normalization of data or ordinal regression | Mann-Whitney rank-sum tests for individual time points with comparisons between H and E, H and S, and S and E | Significant difference at 4 time points for less pain with H than E and S |

S, standard care group; E, empathic attention group; H, self-hypnotic relaxation group.
All patients received local anesthetics.

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