Special Features of Pain Studies

22

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Introduction

The scientific method as a means of knowledge acquisition has a long history. Typically, a study question is formulated, data is collected, and a hypothesis tested. Accordingly, the following is required: precise definition of the problem; the ability to precisely measure variables; and some method to interpret outcome changes as distinguished from the natural history of the disease process. Peculiarities in all three of these areas make the study of pain and pain treatments challenging.

Pain

The commonly accepted definitions of pain all recognize that pain is both complicated and complex. Complicated in that there are multiple dimensions, respecting the sensory and affective aspects, as well as the impact of disuse and disability and the consequent suffering. These factors vary from one disease process to another, from one environmental context to another, and from one individual to another. The complexity results in no small part from the interaction amongst these multiple "moving parts" creating a seemingly unlimited source of variation. As a result, pain itself is not a simple well-defined entity, but rather a personal individualized experience for each patient.

Pain Measurement

Pain measurement methods would be quite straight-forward if the experience was uniform across a given population for a specific disease process. Unfortunately, measurement of subjective or personalized experiences such as pain are far from uniform and often require a compromise between precision and accuracy. *Precision* in measurement is desirable as it can allow for ratio measurements and analysis using parametric methods, thus improving power and minimizing the number of subjects required. Yet over-reliance on unidimensional precise measures such as 0–100 Visual Analog Scales (VAS) for pain intensity, neglecting other pain features, can lead to high variability in responses, reducing the power and often sacrificing *accuracy*. Simpler, more contextual measures, such as a categorical pain report (e.g. the verbal rating scale [VRS], where the subject reports "no pain", mild pain, moderate pain, or severe pain"), while lacking precision, increasing the number of subjects required and demanding non-parametric analysis methods, can often be more accurate. Most awake adult subjects without cognitive impairment can easily relate the intensity of pain to the urgency

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for relief. For example, subjects reporting no pain would not request treatment, whereas subjects reporting severe pain may request highly efficacious pain treatment with rapid onset. Measuring pain with greater precision while maintaining accuracy requires assessment methods that take into consideration both the underlying neurophysiology of nociception, as well as the aforementioned multidimensional impact on the interpretation of the pain experience.

Categorical Versus Ratio Measures

When a subject uses a VAS by placing a vertical mark on a 100-mm horizontal line with a "no pain" anchor at the extreme left and a "worst pain possible" anchor at the extreme right, measurement can be a precise distance in millimeters and is generally accepted to be a continuous variable that is usually treated as a ratio measure. Categorical measures, such as the 4-point verbal rating scale (VRS) have no ratio quality. The "distance" between no pain and mild pain, or mild pain and moderate pain, for example, cannot be assumed to be equal and the numbers assigned to the categories are arbitrary. In other words, the movement from one category to another must be treated with non-parametric methods as these numbers cannot be treated with simple arithmetic operations. If, however, the number of discrete "categories" is increased, can such a verbal report approximate a ratio measure? It may be so in specific circumstances. This effect has been examined by comparing the VAS to the 0–10 numeric rating scale (NRS).

When using the NRS subjects select a number from 0 to 10 (11-pts) where 0 represents no pain and 10 represents the worst pain possible. Patients experiencing pain in different acute pain settings categorized their pain as none, mild, moderate, or severe, then rated their pain on both a VAS and by NRS [1]. In this particular study, the NRS had excellent correlation [$r = 0.88$] with the VAS in young women experiencing labor pain. In other acute pain settings (total joint replacement; thoracoabdominal surgery) results varied despite patients exhibiting understanding of all 3 rating systems. Correlations between the VAS and NRS improved when pain was measured with activity and were generally poorer at rest. The poorest correlation was with the orthopedic pain, in patients who were more often elderly, when experiencing moderate pain at rest [$r = 0.28$]. The reasons for the disparities might include demographic factors, failure to consider the multidimensional nature of pain with subjects attempting to encode features of the pain other than intensity in the unidimensional measure, or perhaps the neurophysiologic underpinnings of nociception. In other words, the degree of stimulation and the subsequent response of nociceptive neurons may not always be linear, but instead might be more exponential, with minimal response until a threshold is reached, then a dramatic response to each incremental increase in stimulation. Regardless of the reasons for the disparity in pain measures, this highlights the need to assure the data is normally distributed prior to assuming the measurements can be treated with parametric methods.

Multidimensional Pain Assessment

It has long been recognized that the affective component of the pain experience, i.e. the unpleasantness, is a significant factor in both acute and chronic pain settings. It is perhaps less well appreciated that movement not only acutely affects the degree of pain, especially in hyperalgesic states, but also that resultant immobility contributes to the development and persistence of chronic pain, in part through microglial pruning of synapses in unused neural pathways. While beyond the scope of this chapter, suffice it to say, functional restorative efforts are crucial. Measures that consider these features within the context of the expectations and goals of the subject more accurately reflect the evolving pain experience. The McGill Pain Questionnaire was arguably among the first to separate out the sensory elements of pain measurement from the affective elements using graded pain descriptors. Since then, a plethora of pain measurement tools have been developed that incorporate these

concepts, as well as measures of function (such as activities of daily living), and are often designed for specific pain syndromes (e.g. neuropathic pain). Guidelines for pain measurement in study settings now uniformly recommend multidimensional assessment; they also typically require patient satisfaction measures. These approaches are also not only practical but essential to the interpretation of treatment response in the clinical setting.

Distinguishing Pain Change Following Treatment from the Natural History of Disease

RCTs Versus Observational Trials

Randomized Controlled Trials (RCTs) are frequently considered the "Gold Standard" for scientific investigation. Through random group assignment, variation in outcome can be accounted for as the result of both known confounding factors and those that have not been considered. This approach is ideally suited for pharmaceutical analgesic trials, where it is often possible, under Institutional Review Board (IRB) supervision, to ethically perform double-blinded placebo controlled or active controlled trials.

Interventional pain studies, in contrast, usually bear a closer resemblance to surgical studies than pharmaceutical trials. Blinding of both the operator and the patient become difficult. Sham surgery or interventions are problematic ethically, but cannot be easily dismissed. Aside from the obvious issues in blinding, the act of intervention itself has meaning and thus affects the meaning response (i.e. the "placebo response"). The more dramatic the intervention, the stronger and longer lasting the effect. Hence the greater reliance in interventional pain studies on prospective observational studies. Yet some form of control is essential since the pain states may wax and wane over time as a function of the natural history of the disease. Major known confounders can be controlled for using techniques such as matched case control approaches, but many other potentially significant confounders may remain at issue. Nevertheless, the most important information, whether the treatment is helpful or harmful, can still be accurately gleaned from well designed, well performed, properly sized, prospective observational studies [2].

In fact, high quality observational studies, often being less contrived and less restrictive in the inclusion and exclusion criteria, may come closer to predicting results that one might expect to see in the actual population that would be treated clinically: "real world" scenarios. Large-scale, well-designed observational studies do not overestimate treatment effects and when compared to RCTs studying the same condition, exhibit less heterogeneity. In other words, the magnitude of change may vary, but while RCTs when repeated frequently give both positive and negative results for the same treatment of the same condition, the observational studies tend to nearly always give the correct "direction" of change [3]. What observational studies may sacrifice in precision can be more than made up for in accuracy: knowing whether a treatment is helpful or harmful.

High Yield Points

- The measurement of pain, as a multidimensional experience, requires multidimensional measurement tools.
- Assuming data is normally distributed, then treating the variables as continuous using parametric methods, may lead to misinterpretation.
- Determining whether a treatment is helpful or harmful is of paramount importance.

Questions

1. Whether assessing the impact of pain in the clinic or in a clinical trial:
   A. The VAS for pain must be the primary outcome measure
   B. The impact on activities of daily living is irrelevant

C. Function and mobility assessment are essential
D. The degree of unpleasantness matches the intensity of nociception
Answer: C

2. The measurement of pain by asking a subject to pick a number between 0 and 10 is:
   A. Consistently equivalent to having the subject place a mark on a VAS scale
   B. Reliable as a ratio measure of pain regardless of the setting or pain model
   C. A unidimensional assessment of a multidimensional problem
   D. More accurate than rating the pain as none, mild, moderate, or severe
   Answer: C
3. Prospective observational trials for interventional pain techniques are:
   A. Not a valid method for acquiring high quality evidence
   B. Ethically unsound, because sham injections can never be used in a study
   C. Often more reflective of the population at risk than RCTs
   D. Efficient because they require fewer subjects than RCTs
   Answer: C

References

1. Hartrick CT, Kovan JP, Shapiro S. The numeric rating scale in clinical pain measurement: a ratio measure? Pain Pract. 2003;3:310–6.
2. Hartrick CT. Quality assessment in clinical trials: considerations for outcomes research in interventional pain medicine. Pain Pract. 2008;8:433–8.
3. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med. 2000;342:1887–92.