Variability in Human Drug Response
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Pain - How to standardize a subjective measure

Eija Anneli Kalso

Pain Relief Unit, Department of Anaesthesia, Helsinki University Central Hospital, Helsinki, Finland.

ABSTRACT

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". Consequently, pain as experienced by the patient itself is always a subjective measure and its quantification is not as straightforward as measuring blood pressure. However, good tools have been developed for clinical and research purposes. The sensitivities of various visual analogue and categorical verbal rating scales to measure both pain intensity and pain relief have been validated. In order to standardize these measurements the pain intensity and pain relief are examined at a certain state i.e. either at rest or during that activity that is most likely to produce the worst pain. Pain questionnaires have been developed to provide more information about the different qualities of pain: sensory-discriminative, affective-motivational and cognitive-evaluative.

The sensory qualities of pain can also be analyzed using standardized stimuli to evaluate mechanical allodynia (von Frey hairs), thermal hyperalgesia (thermotest) or pressure pain thresholds. These methods have shown to be useful diagnostic tools. They are also used to assess treatment effects in both acute and chronic pains. More sophisticated neurophysiological and neuroimaging techniques are available but not for routine use.

Key words: visual analogue scale, verbal rating scale, McGill Pain Questionnaire.

Correspondence: Dr. Eija Kalso, Pain Relief Unit, Department of Anaesthesia, Helsinki University Central Hospital, Haartmaninkatu 4, P.O. Box 260, FIN-00029 HYKS, Finland, Tel: +358-9-471-5640, Fax: +358-9-471-5641, Email: Eija.Kalso@huch.fi

INTRODUCTION

Pain is by definition "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" and therefore always a subjective measure. Several tools have been developed to measure pain. In order to use these tools adequately we have to understand of what components the total pain experience is made of. The quantity and also the quality of tissue injury is an important factor: more extensive

trauma causes more pain which also takes longer to heal. The final report of pain is further modified by the patient's previous pain experiences and by the current emotional state.

TOOLS TO MEASURE PAIN

The sensory qualities of pain can be analyzed using standardized stimuli to evaluate mechanical allodynia (von Frey hairs), thermal hyperalgesia (thermotest) or pressure thresholds. These methods have been shown to be useful diagnostic tools. Sophisticated neurophysiological and neuroimaging techniques can quantify the neurophysiological responses of painful stimuli and localize the respective brain areas that are activated. However, the total experience of pain, as a subjective experience, can only be evaluated by the subject of pain, the patient.

The sensitivities of various visual analogue and verbal rating scales to measure both pain intensity and pain relief have been validated [1].

Verbal rating scales

The oldest of the standard measures is the four-point pain intensity category scale (Table 1). However, it may not have enough levels to allow the patients to accurately describe their pain level. In addition, the numerical scores for the categories are arbitrarily set to equal step integers without evidence that the levels of pain to which they correspond are spaced apart an equal number of discernible difference units. It has been suggested that there is a greater difference for patients between severe and moderate pain than between moderate and slight. More extensive lists of pain descriptors have therefore been developed (Table 1) [2,3].

Table 1.
Categorical scales for pain intensity

4-point scale	8-point scale
none	no pain
mild	just noticeable
moderate	weak
severe	mild
	moderate
	strong
	severe
	excruciating

Pain relief category scales have been reported to be more sensitive to small reductions in pain compared with the pain intensity category scales [4]. Categorical pain relief scales rely on the patient's memory of pain at the baseline period. This does not seem to be a problem in short studies (a few hours) but may reduce reliability of relief data in longer studies for reasons that will be discussed later.

Visual analogue scales

A visual analogue scale is a line with "least possible pain" labelled at one end and "worst possible pain" at the other. The patient is asked to mark the line at a point corresponding to his present pain level [5]. Visual analogue scales are continuous and thus relatively free from some of the biases that may complicate category scales such as patients using as much of the range of words as possible. Uninformed and especially older patients may, however, have difficulties in understanding the meaning of a visual analogue scale. Horizontal VAS scales [6] between 10 and 15 cm in [7] have been suggested to be the most reliable. Visual analogue scales can be used to measure both pain intensity and pain relief.

Wallenstein *et al.* [8] compared the ratings of 257 patients using the four category pain scale to the VAS pain scale and showed that the four categories were not far from equal spacing. Also the pain relief category scales were shown to be rather evenly spaced, relative to their equivalent VAS ratings [8].

Littman *et al.* [4] compared the pain intensity category, relief category and pain intensity VAS scales in 20 clinical trials with about 1500 patients receiving analgesics or placebo. The sensitivities of the scales to detect a treatment difference decreased in the following order: the relief category, the VAS pain scale and the pain intensity category scale. The three scales gave the same overall conclusion in 17 of the 20 studies.

In the same study Wallenstein *et al.* [8] showed that a very simple measure "pain is at least 50% relieved" is highly correlated with both the categorical and VAS ratings. The use of this simple measure as part of the analysis of pain relief would enable the combination and comparison across different studies using meta-analytical methods.

The McGill Pain Questionnaire

The McGill Pain Questionnaire (MPQ) was designed to assess the multidimensional nature of pain experience, not just pain intensity, of chronic pain problems. The Pain Rating Index (PRI) of the MPQ includes 20 groups of pain descriptors [9]. Each group assesses a different quality of pain experience. These subclasses are further grouped into three subscales designed to assess the sensory-discriminative, affective-motivational and cognitive-evaluative dimensions of pain [10, 11]. Because the PRI provides quantitative measures of multiple pain dimensions it can be used to evaluate the effectiveness of pain treatments.

Escape medication

Consumption of escape medication is often used as a primary measure in analgesic studies. In many clinical studies the protocols for taking escape medication have serious flaws. The escape medication should be clearly defined as to which drug should be given and when. If the decision is left to the nurse as "when needed" significant delays may take place. An important improvement in this respect is the use of patient controlled analgesia (PCA) which allows the patient to self administer opioids when needed intravenously. This method has been used to test the effectiveness of local anaesthetic blocks or non-steroidal anti-inflammatory drugs in postoperative analgesia [12-14]. A few words of warning are necessary, however. If the consumption of morphine is regarded as a measure of pain experienced by the patient then all patients should aim at a similar state of pain relief. If the VAS-values are different between the two study groups, the value of the consumed dose of morphine is less reliable. The patients may prefer pain to nausea caused by morphine. It should also be taken into account that analgesics may potentate each others' effects.

MEASURES TO STANDARDIZE THE ANALYSIS OF PAIN

As acute and chronic pain states represent pathophysiologically very different entities these conditions are discussed separately.

The noxious stimulus

The interindividual variation in response to noxious stimuli is great. Individual pain thresholds (when a potential injury is noticed as painful) and pain tolerance (how much pain the person can stand before taking a pain killer) are controlled by the individual's physiological, behavioural and cultural factors. Even if most of the demographic variables are controlled e.g. age, gender and ethnicity the variation still remains significant. Thus it is essential to standardize the noxious stimulus. Nerve compression pain is very intense as is ischaemic pain. Wound pain is less severe and can be almost absent when the patient is at rest. Thoracotomies are very painful postoperatively whereas operations for inguinal hernias rarely cause severe pain. Postoperative pain is the most commonly used set up to study acute pain. Molar extraction is perhaps the most commonly used model. As the operation is often performed to both sides the patient can serve as his own control. In the next examples, however, pain following thoracic surgery is used to show how pain measurement can be standardized.

Some of the factors that need standardizing in studies on postoperative pain are given in Table 2.

Table 2.
Factors affecting postoperative pain measures

type of surgery
surgical technique
premedication
type of anaesthesia
escape medication
timing of pain measurement
measurement of pain at rest/during movement
who performs the measurements

The significance of the type of surgery is shown in Figure 1. Thoracic surgery can be performed either by opening the chest wall (thoracotomy) or as videoaoassisted thoracoscopic surgery which causes significantly less trauma than thoracotomy. Figure 1 shows the evolvement of pain after these two types of thoracic operations. In both groups the patients were able to self administer as much intravenous morphine as they needed using a PCA device. In spite of this and the fact that the thoracotomy patients were given intercostal nerve blocks before closure of the thoracotomy, the mean VAS-pain intensity ratings were significantly lower in the thoracoscopy group.

Even today many studies on postoperative pain do not mention whether pain was measured at rest or during movement. Figure 2 shows the striking difference in pain intensity after

thoracotomies when the pain is asked either at rest, when the patient moves or coughs. It is not only that the patient's report on pain intensity varies between these three measurements but these situations also analyze two different pathophysiological states of pain. The pain at rest usually represents the dull constant C-fibre-mediated pain whereas the pain which is evoked by movement or coughing is connected to hyperalgesia. As modern analgesics have more selective targets for actions these aspects of pain analysis become increasingly important

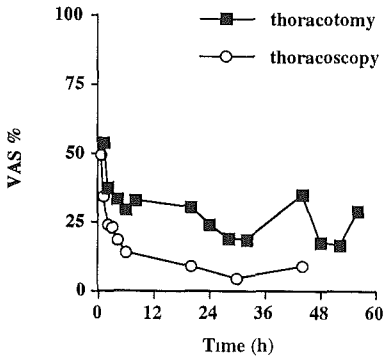

Figure 1. Pain intensity (% of the maximum on a VAS scale of 0-100) after thoracotomies and video-assisted thoracoscopies. Intercostal nerve blocks were performed at the end of surgery following thoracotomies. The patients were able to self administer morphine intravenously using a PCA (patient controlled analgesia)-device. Data has been combined from Perttunen *et al.* [12,14].

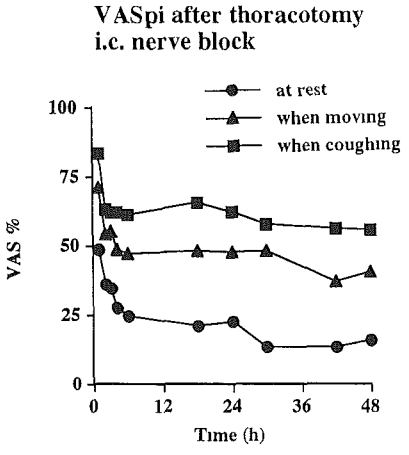

Figure 2. Pain intensity (% of the maximum on a VAS scale of 0-100) after thoracotomies. Intercostal nerve blocks were performed at the end of surgery. The patients were able to self administer morphine intravenously using a PCA (patient controlled analgesia)-device. Pain was asked when the patient was at rest, during movement and when coughing. Data is from Perttunen *et al.* [13].

Standardizing the painful state is equally if not even more important in chronic pain. The pathophysiological mechanisms behind different chronic pain states may be quite different [15]. A good example is neuropathic pain. Contrary to nociceptive pain neuropathic pain usually does not respond well to non-steroidal anti-inflammatory drugs or opioids. Instead, pain relief is achieved with antidepressants and anticonvulsants. Drugs that reduce hyperalgesia may have no analgesic effects in nociceptive pain.

In acute pain the time from tissue injury is important as pain decreases with time. In chronic pain the constant pain usually stays and is aggravated by different factors. The patients should therefore keep a pain diary and mark the intensity of pain 2-4 times a day. Again, in order to appreciate how much variation the individual patient may have in the pain experience

the pain intensity is assessed as present pain, average pain, least and most intense pain. The time of the day when the pain analysis is made can also be important. Patients with rheumatoid arthritis suffer from stiffness and pain particularly in the morning. Many other chronic pain patients, however, report that their pain gets worse in the early evening hours.

Both the patient and the person who assess pain and pain relief should be trained to use the tools of measurement.

Standardizing initial pain intensity

Assay sensitivity and test power can be increased by selecting patients with sufficiently high initial pain intensity. A good example is a study by Bjune *et al.* [16] who studied pain relief after Caesarean section in a randomized, double blind, single oral dose parallel group comparison of paracetamol+codeine, paracetamol only or placebo. Of the total of 108 patients who completed the study 49 patients had moderate initial pain (visual analogue scale 40-60/100) and 59 severe pain (VAS >60/100). The latter group showed both good upside sensitivity i.e. two active drugs were differentiated, and downside sensitivity i.e. the active drugs showed better pain relief than placebo. On the other hand, no differences were revealed between the three groups in any of the efficacy variables in the group of patients who had moderate baseline pain. Similar results have been published recently [17,18].

PRESENT VS PAST PAIN

The present pain should always be included in the analysis as the situation can be standardized and as the intensity of present pain may affect the patient's estimation of previous pain. Present pain is usually asked in studies on acute pain and during the patient's visits in studies on chronic pain. The reason for not relying on the patient's memory for previous pain are discussed below.

Memory for pain

Memory for pain is often implied in assessment instruments used in research.
Current pain states seem to influence estimates of past pain intensity in a systematic manner. In a study on breast cancer patients [19] the women were allocated into two groups according to whether they had or did not have chronic treatment related pain at 12 months from surgery. Those patients who did not have chronic pain (n = 69) remembered their past postoperative pain at 12 months as significantly ($p<0.001$) less severe compared with how they remembered it at 1 month. The patients who had developed chronic treatment related pain (n = 15), however, remembered the past postoperative pain as significantly more severe when asked at 12 months from surgery compared when asked at 1 month after surgery. Similar results have previously been reported by Eich and colleagues [20] who studied patients with chronic headaches of myofascial origin. When the present pain was high, patients rated their maximum, usual and minimum levels of pain as being more severe than what the hourly pain diaries indicated. When their present pain intensity was low, the same patients remembered all 3 levels of prior pain as less severe than they actually had been. Linton *et al.* [21] have suggested that chronic pain patients may significantly overestimate recalled baseline pain ratings.

Modulation of memory by emotions

Emotions exert strong assimilative effects on memory [22] and could therefore be important in the processing of pain memory. Hunter *et al.* [23] have indicated that high affect may lead to a distortion and overestimation of pain in memory. Kent [24] examined the role of affect in memory for pain in dental patients. He found that anxious and non-anxious patients reported similar pain intensities when asked immediately after surgery. However, both the expected pain intensity levels before surgery and the recalled pain intensities at 3 month follow-up as reported by the anxious patients were significantly higher than the actual pain or the respective values reported by the non-anxious patients

Redelman and Kahneman have shown that individuals vary substantially in the total amount of pain they remember from painful medical treatments. Patients' judgment of total pain seems to be strongly correlated with the peak intensity of pain ($p<0.005$) and with the intensity of pain recorded during the last 3 minutes of the procedure ($p<0.005$). The duration of the painful procedure, however, does not correlate with the future memory of the past pain.

CONCLUSIONS

Only some of the factors that are important when attempting to standardize pain measurement have been discussed above. An excellent summary with a comprehensive list of references on this topic has been provided by the International Association for the Study of Pain [25].

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Discussion: Pain - How to standardize a subjective measure

L. Aarons:
Is it true that the pain relief scale and the pain intensity scale measure different things?

E.A. Kalso:
In a way these scales measure different things, because one is for intensity and one is for relief. But if you mean that they do not correlate with each other, there is evidence to show that intensity and relief go in opposite directions. To validate the pain relief scales against pain intensity scales it is possible to calculate the pain intensity difference, which you can use in more chronic trials if you want to assess the present pain before treatment and then at different time points during the treatment.

M.M. Reidenberg:
These methods that have been presented have enabled the scientific work on pain to advance very well. Our experience when trying to translate these into useful day-to-day patient care in a medical service is that they don't work because of staff attitudes of doctors and nurses towards pain. For most other areas of medicine and clinical pharmacology, procedures that were developed for research purposes can move over into clinical care with reasonably effective utilisation in daily care. Pain is different and the challenge that we have in addition is to come up with ways to assess pain in ordinary routine medical care that will be accepted and used by doctors and by nurses.

E.A. Kalso:
That is a very important point. In Sweden these scales have been introduced in daily practice. Following the quality programme at the Karolinska Hospital in Stockholm, for any patient who shows more than three times per day a pain intensity of 4 out 10 on the visual analogue scale, a pain specialist should be consulted.

M.M. Reidenberg:
After the requirement was instituted, did the frequency at which the pain levels were recorded at this height change?

E.A. Kalso:
I do not have this information.

J. Urquhart:
One of the great teachings to come out of the hospice movement, confirming observations of good doctors from long before that, was that the continuity of pain analgesia is a very important aspect and one has to consider that pain recurs in cycles. I wonder if you could comment on that.

E.A. Kalso:
This is a very complicated situation. If the pain is constant, then slow-release drugs or drugs that are given on a regular basis are fine. But most of the patients also have pain which is

aggravated by certain movements, or what we call insidious pain. And therefore the patients also need medication which they can take when they feel the pain. On the other hand, the patients want to balance between adverse effects and pain relief. The most important thing is that the patient is in control over the pain relief, and the drug is available when he needs it. And that is why, for example, it has been shown that the consumption of morphine can be decreased using patient controlled analgesia.

P. Rolan:
In our headache clinic, we routinely ask our patients to fill in a diary before their first appointment. We started that because we found it very difficult to reconcile some of the patients' histories. They are completed very well, but it is almost always that the diary shows less pain than the patients report to me. This is the opposite direction to the findings you presented. My interpretation is that patients have often waited a long time to see the doctor, and they want to really impress him how much they are suffering, so that the doctor will take them seriously and give them good treatment. And that is why I found the diary is absolutely essential. It is obviously looking at different populations and these are not really chronic pains, but recurrent acute pains.

E.A. Kalso:
This is true in most of the patients, but it really goes in both directions. We did a study for patients who had been operated for breast cancer and some of them developed chronic pain and others did not. We followed these women from the time before surgery and for a year after surgery. Those women who had chronic pain at one year remembered that their previous acute post-operative pain had been actually much more severe than it had been, whereas those women who had no chronic pain remembered their previous acute post-operative pain had been much less than what it had actually been.

G.T. Tucker:
Where are we now in terms of using biochemical indices of measurement of pain, like endorphins or encephalins? One expects an inverse relationship between their levels and the degree of drug requirement.

E.A. Kalso:
I do not think we have advanced much since the original studies done in Sweden in the early 80s, where it was shown that there is an inverse correlation between the levels of endorphins in the cerebro-spinal fluid and the amount of analgesics the patients needed. Nevertheless, biochemical markers are very insensitive, because they may not only correlate with the pain, but they also are released by stress factors and other factors not connected to pain.

A. Breckenridge:
Could you please add some data on this intriguing statement about the different cultural and ethnic backgrounds to the perception of pain?

E.A. Kalso:
The study which is most often quoted compared a Northern European population, a Southern European population, and a Jewish population. The expression of pain varied significantly. It

was less in the Northern European population, the highest in the Southern European population, and in the Jewish population it changed, first it was high, but when the population realised what the question was about, their pain expression went down.