

How to define a Minimal Clinically Individual State (MCIS) with pain VAS in daily practice for patients suffering from musculo-skeletal disorders

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Received on July 12, 2004; accepted in
revised form December 29, 2004.

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Key words: Clinical metrology,
outcome measures, state criteria.

ABSTRACT

Objectives. Pain is frequently the primary variable in symptomatic clinical trials for the evaluation of rheumatological disorders. The protocol of such trials mention a minimum level of pain as an entry criterion [e.g. a level above the Patient Acceptable Symptoms State (PASS)] and the changes in pain as the primary variable. Usually, the results are expressed at a group level as the mean changes in pain. However, the presentation at an individual level and, in particular, the percentage of patients with a Low Disease Activity State at the end of the study seems more clinically relevant.

Pain is usually evaluated using a continuous variable such as a 0-100 visual analogue scale. The cut-offs permitting one to define both the entry criterion and the LDAS are not well established. The objective of this study was to evaluate such cut-offs using a patient-derived perspective.

Methods. Study design: cross-sectional study. Patients: consecutive out patients suffering from chronic rheumatic diseases familiar with the use of a VAS to evaluate their level of pain. Data collected: two questions were asked the patients at the end of the visit: "Based on the experience you have because of your chronic rheumatic disorder, could you please specify the level of pain below which you consider your disease as inactive? Moreover, could you please also specify the level of pain above which you consider taking a pain killer?" Before answering the second question, it was explained to the patient that their answer to the second question could be similar to their response to the first one. For the two questions, the cumulative percentage of patients (disease inactive and pain killer intake) were calculated for each level of pain.

Results. The underlying disease of the 137 evaluated patients (mean age: 57 ± 16 and female sex: 76%) was rheumatoid arthritis (n = 59), ankylosing spondylitis (n = 19), SLE (n = 2), back pain (n = 20), or peripheral osteoarthritis (n = 37). The mean disease duration was 12 ± 10 years. At the time of the study, the current level of pain evaluated on a 0-100 VAS was 33 ± 22. The LDAS was

49, 36 and 25 for our patient population at the 25th, 50th and 75th percentiles, respectively. The pain killer intake level was 32, 48, 64 at the 25th, 50th, 75th percentile respectively.

Conclusion. This study suggests that LDAS and PASS may be distinct concepts. The methodological approach adopted here could be of interest for specifying the minimum level of symptoms at entry in a symptomatic trial (PASS) and also to present results in terms of the percentage of patients in good condition (LDAS) at the end of a trial.

Introduction

Pain is often the primary variable to evaluate activity in chronic musculo-skeletal diseases (1, 2). In clinical trials, quantification of pain is needed to improve data exchange at the group level (3) and is usually reported as the mean and standard deviation of changes in pain. At the individual level it is recommended to facilitate doctor-to-nurse or doctor-to-doctor communication (4). As emphasized at the 6th OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) meeting, a major objective is to include the patient's perspective, which can influence clinical decision (5,6). Because of the suspected poor inter-patient reliability of the evaluation of pain, it is considered as proper to use VAS only to quantify changes in chronic pain.

Such a tool (0-100 mm VAS) is very powerful to detect changes under the influence of active therapy (discriminative capacity). However, the clinical relevance of such a continuous variable still remains questionable. The definition of cut-offs permitting one to switch such a continuous variable into a dichotomous variable might be of interest for at least two reasons:

- The eligibility criteria usually refers to a minimum level of pain permitting one to evaluate the study drug. Such a "minimum level of pain" is required to justify initiation of the study drug. In other words, only patients in whom such a treatment is justified should enter the trial. Such justification should be based on the patient's perspective and refers to

the concept of Patient Acceptable Symptom State, i.e., the level of pain above which the patient will spontaneously take a pain killer.

- The outcome measure in symptomatic clinical trials usually refers to the concept of changes and/or responders. Therefore, the results are most frequently reported in terms of mean changes or (less frequently) in terms of the percentage of patients with a relevant change. Such "relevant change" requires one to switch the continuous variable "change in pain VAS" into a dichotomous variable "response is defined by a change of at least X". X is usually defined as a relative change of 50%. Besides this relevant concept of the responder ("to be better"), another concept is emerging that is probably more meaningful to monitor painful patients in daily practice: the one of "to be in good condition under therapy whatever the change from baseline".

This concept – known as the Low Disease Activity State (LDAS) – also switching the continuous variable "0-100 mm VAS" into a dichotomous variable "low disease activity" (or good condition), which is defined by a value of pain below X. To our knowledge, such a cut-off X is not well determined (7, 8). Moreover, it has not been established whether the concept of PASS (Patient Acceptable Symptom State) justifying a pain killer intake by the patient is equivalent to the one of LDAS (Low Disease Activity State). These preliminary observations prompted us to conduct a prospective study

based on the patient's perspective in order to evaluate these two concepts and to compare them.

Patients and methods

Patients and data collection

All patients suffering from a chronic musculoskeletal condition and seen at the outpatient clinic by the investigators (MD=Dougados, GF = Falgarone) were systematically included over a chosen period of 4 months. Data were collected in an open prospective study in the outpatient clinic during this period. We recorded age, sex, aetiology of pain, disease duration, and analgesic intake. Patients were included if they suffered from either inflammatory rheumatic disorders (rheumatoid arthritis, spondylarthropathies, systemic lupus erythematosus) or mechanical disorders (degenerative back pain, peripheral osteoarthritis). The single exclusion criterion was the patient not being able to show a level on an horizontal visual analogue scale using a slide rule. The level of pain for the last week prior to the visit due to chronic rheumatism was collected using a VAS scale with a range from 0 to 100 (101 values).

Evaluation of MCIS or PASS

Two questions were asked in order to estimate the pain level below which a low disease activity state could be admitted, and pain that required drug intake. Two questions were asked, to determine: i) the minimum level of acceptable pain, i.e. "Based on the experience you have because of your chronic rheumatic disorder, could you please specify the level of pain below which you consider your disease as inactive;

and ii) the level of pain justifying an analgesic intake, i.e. "Could you please specify the level of pain above which you would consider taking a pain killer?"

Analysis

The first step was to calculate the mean, median and standard deviation of the data collected. The second step was to draw divisions in percentiles to find the 75% patient value. This value was chosen because it is the point at which the curve of the logistic regression used in previous works flattened (7) and this seemed to represent a realistic goal to aim for. For each value, linked factors were studied, e.g. age and sex. Variance analyses (ANOVA) were calculated using an SAS package (SAS Institute Inc., North Carolina, USA).

Results

Patients characteristics

During the 4-month period, 137 patients were included in the study by the two investigators. As shown in Table I, 104 women and 33 men were recruited, (age 57 yrs., SD 16); 80 patients suffered from inflammatory chronic rheumatism and 57 patients suffered from degenerative disorders. The mean disease duration was 12 years (SD 10, range 1 – 57 yrs.). The distribution of patients between the investigators was 2/3 for MD, 1/3 for GF, and the demographic characteristics were similar between the populations studied by each investigator. The global population was broadly identical to the one usually treated by the two investigators. Interestingly, less than 1% of the patients were not able to choose a level on VAS, even if they did feel pain, so they were excluded (2 out of the 137 patients). The mean pain value at inclusion was 33 (SD 22).

Value of pain, level of discomfort and level of pain requiring drug

The mean VAS pain level before analgesic treatment was 62.18 SD 23. The median level of acceptable pain (LDAS) was 36, with a mean of 40.5 (SD 13.73, range 1 – 100). The median level of pain justifying analgesic intake

Table I. Patients characteristics.

Age (years)	57, SD 16
Disease duration	12, SD 10
Sex (female/male)	104 F/ 33 M
Diagnosis (total)	137
Inflammatory rheumatic disorders	80
Rheumatoid arthritis	59
Spondylarthropathies	19
Systemic lupus erythematosus	2
Mechanical disorders	57
Degenerative back pain	20
Peripheral osteoarthritis	37

(pain killer intake) was 48, with a mean of 51.56 (SD 14.92, range 1 – 100). These levels of LDAS and pain killer intake are represented in Figures 1 and 2 respectively, using a cumulative curve of percentage. As represented, the LDAS was 49, 36 and 25 for our patient population at the 25th, 50th and 75th percentiles, respectively (Fig. 1). The pain killer intake level was 32, 48 and 64 at the 25th, 50th and 75th percentiles respectively (Fig. 2).

Co-factors

For each value, we observed no influence of disease duration, age or sex. For each value of pain we observed no difference for the background disorder, comparing the inflammatory group (80) with the degenerative group (57). We observed no difference between pain scores according to which investigator asked the questions. The coefficient of correlation between the two levels of pain (requirement to drug intake or acceptable state) was 0.700 with a $p < 0.001$, as represented in Figure 3.

Discussion

Our study suggests that the evaluation of the acceptable state of subjective symptoms such as pain should definitively take into account the patient's opinion. This evaluation should take into account the absolute value of the variable below which the patient estimates his/her status as acceptable, as well as the value of the variable above which taking a medicine in order to control the discomfort level is considered by the patient.

The patient population recruited for this study reflects the patients observed in a department of rheumatology. The observed results were not influenced by factors such as the patient's demographics or underlying disease.

This study also confirms the feasibility of measuring the level of pain using a simple Visual Analogue Scale, since only 1% of the patients in this study were unable to show their level of pain using such tool, even they did feel pain. Therefore the horizontal slide rule has once again been confirmed to be an easy-to-understand tool.

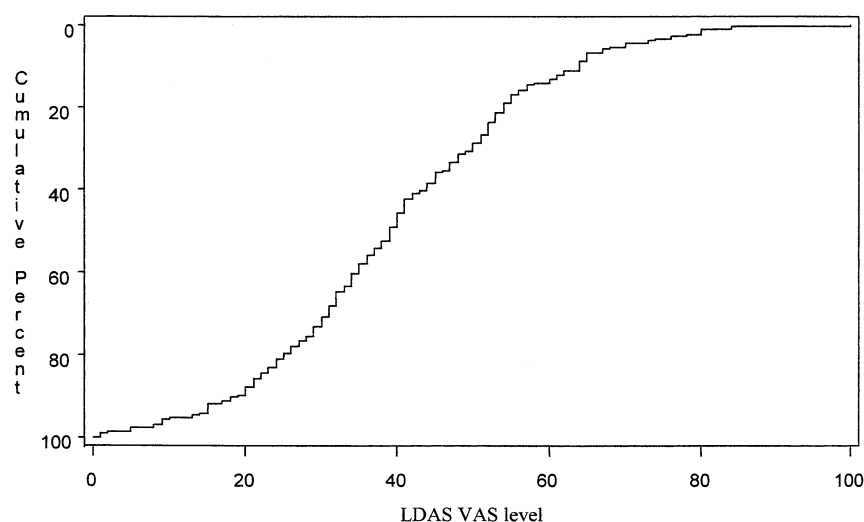


Fig. 1. Cumulative percentage of LDAS: Based on the experience you have of your chronic rheumatic disorder, could you please specify the level of pain below which you consider your disease as inactive ?

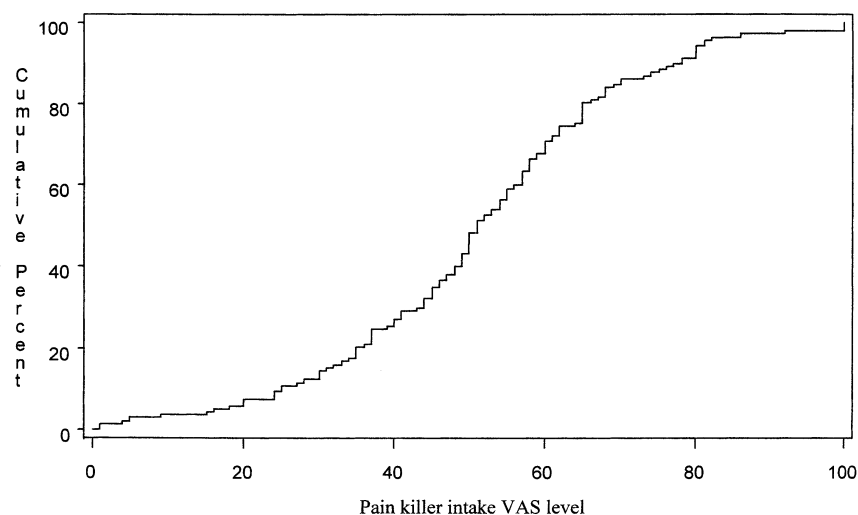


Fig. 2. Cumulative percentage of value for pain killer intake: Could you specify the level of pain above which you would consider taking a pain killer ?

It is widely acknowledged that the methodology to detect a cut-off (MCIS or LDAS) for a subjective symptom as pain should take into account the patient's perspective (5,6). Such a methodology was applied in the present study in a group of patients with either inflammatory or degenerative pain.

The question still remaining is the statistical method to be used in order to propose a cut-off. Our study clearly emphasizes the large inter-patient variability involved. This variability suggests that the proposed cut-off might not be relevant for daily practice use. However, this cut-off might be of inter-

est for measuring pain at the group level and for use in clinical trials.

Interestingly, in some patients the "acceptable level" of pain was lower than the pain level requiring an analgesic, while in many others the reverse was true. This raises the point that the concept of "an acceptable level of pain" seems to be complex and the LDA [which takes into account pain but also biological markers (8)] must be considered as a distinct concept from that of PASS.

Taking into account all of these results, we suggest that a minimum level of pain of 60 (on a 0-100 mm VAS) should

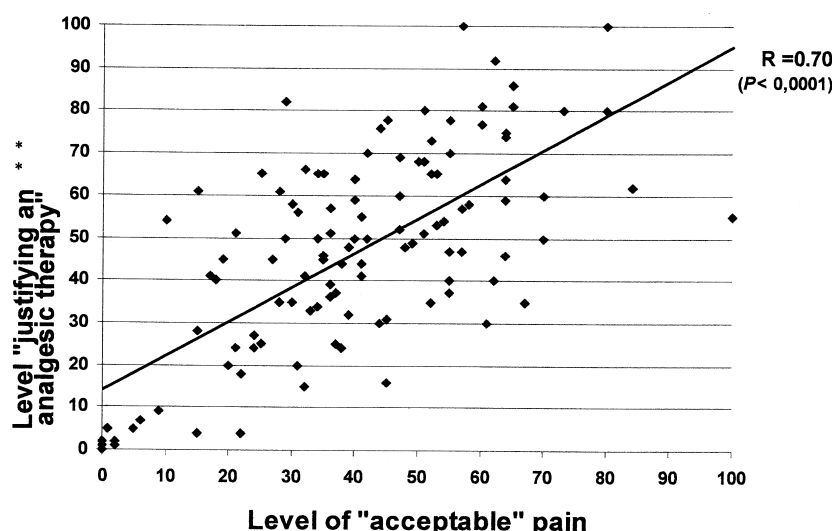


Fig. 3. Correlations between the two levels of pain: *Level of pain considered by the patient as the "maximum acceptable" in order to maintain personal and social activities (LDAS). **Level of pain considered by the patient as significant enough to take measures to control such discomfort (p value for pain killer intake).

be used as an inclusion criteria for evaluating treatment strategies for pain. This cut-off is proposed because 75% of our patients [which seems to be an expert recommendation (7)] considered taking a medicine to control pain when the level was over 64. Moreover the presentation of the results should include the percentage of patients at the end of the study with a level of pain below 25. This cut-off is proposed because at least 75% of patients considered their status as "acceptable" when their pain level was below 25. These tools could easily be used, even if a re-

cent study seems to consider that Rheumatoid arthritis Quality of Life Scale (RAQLS) and the Health Assessment Questionnaire (HAQ) are the best instrument for measuring disabilities in patient with rheumatic disorders (9). Moreover, biological parameters such as DMARDs for inflammatory conditions should also be taken into account in these studies. Further research conducted in different sets of patients suffering from other painful conditions and/or with different cultural backgrounds and/or languages should permit us to better specify the proposed

cut-offs and confirm the use of VAS to estimate PASS.

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