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Editorial comment

The value of critical values from normative data

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In this issue of the *Scandinavian Journal of Pain*, Scaramozzino et al. [1] present percentile normative values of nociceptive withdrawal reflex and pain thresholds to different electrical stimulation paradigms. The authors suggest that percentiles from a distribution of electrical pain and reflex thresholds from pain-free subjects could be used to detect central hyper- and hyposensitivity in individual patients.

1. Distribution of thresholds

Pain and reflex thresholds from single and repeated electrical stimulation in 300 pain-free subjects were recorded. Summary statistics as well as multivariable analyses identifying important covariates have been published previously based on the same sample [2]. Age was shown to have a statistically significant effect on the subjective pain threshold. The reflex threshold was statistically significantly associated with body-side (dominant or not). No differences between men and women were found.

The purpose of this follow-up analysis is to provide estimates of critical normative values that can be used in research on mechanism based chronic pain treatment as well as in clinical practice for assessment of widespread hypersensitivity and hyposensitivity in individual patient. Information on the distribution of electrical pain and reflex thresholds in pain-free volunteers is without doubt of value for pain research. An obvious question is, however, how to define critical values as a "diagnostic tool" in individual patients with chronic pain and in which way such critical values can actually be applied in practice.

Normative percentile critical values for hyper- and hyposensitivity were estimated by quantile regressions adjusting for a number of covariates. Percentile estimates are presented separately for age groups and body-side.

2. Which percentile indicates a disturbance?

Can reference values from pain-free subjects be used as the sole basis for identification of hyper- or hyposensitivity in an individual patient? Which percentiles to use as cut-offs appropriate to correctly classify the sensitivity of a single individual is less than obvious. It could be argued that in a sample of pain-free individuals all subjects' thresholds should be regarded as observations within the normal range. The identification of percentiles in the pain-free population is thus only a small step forward.

Uncritically defining for example the 25-percentile as a cut-off for classifying subjects as hypersensitive does not seem appropriate. Applying the corresponding definition of hyposensitivity would imply that 50% of a pain-free population would be regarded as hyper- or hyposensitive and that only half of the population responds within the "normal range" to electrical pain stimuli. It is certainly not appropriate to define someone as hyposensitive because approximately 75% of the population in question is more sensitive to electrical pain stimuli than he is.

The authors correctly state that adoption of extreme values is more likely to correctly identify a critical observation and thus reduce the probability of false positive findings. On the other hand, the choice of an extreme value increases the probability of a false negative classification.

It would undoubtedly have been of interest to assess the sensitivity and specificity of different choices of critical values, but this cannot be done with a sample of pain-free subjects only. Indeed, a sample of chronic pain patients should also be studied. That would give the opportunity to assess positive and negative predictive values in the patient population in question and thereby usefulness in practice.

3. Representativity

Even agreeing that reference values from a pain-free population can be useful for the purpose of evaluating a single patient, a critical assumption is that the sample of 300 subjects can be regarded as representative of the population of pain-free individuals. Little or nothing is said about recruitment to the study and it is therefore difficult to conclude. The subjects are obviously not randomly selected. In fact according to the previous paper on the same sample patients were recruited by advertising in local Swiss newspapers and various other announcements [2]. Selection bias can thus not be excluded. Individuals regarding themselves as very sensitive to pain would hardly volunteer for the experiment. Validity in a non-European population might also be questioned. A minimum requirement for detection of central hyper- or hyposensitivity in an individual patient based on the percentile estimates is an identical test situation including a training session as described.

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4. Precision

The precision of estimates depends on sample size as well as variability between individuals. Presumably inclusion of a large sample of individuals would not have been feasible. Nevertheless, a sample of 300 subjects seems rather small as a basis for normative data and the small number of subjects included could be problematic with regard to precision of the percentile estimates in subgroups. Lack of precision of estimates is probably of minor concern compared to the previously mentioned risk of selection bias as well as the choice of critical values or cut-offs. However, an assessment of variability, for instance by adding 95% confidence intervals, would have been welcome. It is also of note that the same investigator performed the experiments in all 300 patients. Any between investigator variability therefore remains unknown.

5. Clinical usefulness

Definition of critical values by means of percentile estimates is a first step towards identifying cut-offs appropriate for evaluation of individual patients. Any added practical value compared to information on distributional characteristics based on summary statistics has however yet to be demonstrated. If critical values are to be useful as a kind of diagnostic tool, further research should include assessment of sensitivity and specificity using different cut-offs. Such research would imply measuring thresholds also in samples of patients with chronic pain conditions. This effort would add valuable information on the practical usefulness of critical values based on electrical pain and reflex thresholds.

References

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