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Commentary

Underpowered clinical trials: Time for a change

Chronic low back pain is associated with degenerative changes of the intervertebral discs in the lower part of the spine [4]. The prevalence of this degeneration is high and related to age and sex and may go up to 60% in a 70-year-old male population [5]. The pathological basis of this discogenic pain may lie in internally disrupted intervertebral discs, in particular, sensitized annular tears [2]. These tears can extend the outer portion of the annulus and both mechanical and chemical stimulation of nerve fibers can occur. The outer part of the disc, the annulus fibrosis, is innervated by the surrounding nervous tissue [1]. In this issue Kvarstein et al. [3] tested a novel flexible radiofrequency electrode, the discTRODE TM, which can be directly placed in the posterior and posterolateral mid annulus of a painful disc. No objective and randomized studies are published about this new tool. The study is well designed, however, there are some significant problems with the execution of this study which are discussed below.

The first problem is the insufficient inclusion of the patients. The sample size of this study was based on the outcome of a pilot study and the Pauza study [7]. The calculated sample in each group was 25 patients. In a period of two and half years 74 patients were recruited for this study out of more than 700 referrals. Only 20 patients were included in the study. The second problem lies in the way the original design of this study was executed, i.e. the inclusion of patients. Patients were supposed to be selected based on unremitted low back pain for more than 6 months and a pain intensity >5 (maximum 10). In spite of these inclusion criteria, patients with a very low pain intensity were included and evaluated in both groups. This is a major problem in several ways. An initial low pain intensity does not justify an interventional therapy with potential danger, such as infection of the intervertebral disc. Moreover, if the subjective pain intensity is so low one cannot expect much improvement of an intervention. For that reason a post hoc analysis was performed with the 4 patients with a too low baseline pain level excluded. This fact reduces the study population to only 16 patients and thus also the power of this study.

The third problem is the inconclusiveness of the results. The primary outcome, an 11-point numeric rating scale (NRS), showed only a slight difference between both procedures. The three secondary outcome measures, i.e. experienced pain, health-related quality of life, and functional ability, point in the same direction. There seems to be a positive effect for the active treatment group 12 months after the procedure. At twelve months follow-up, 5 patients (50%) of the active treatment group experienced at least 50% pain reduction. Only one patient of the sham group reported more than 50% pain relief. We observed the same trend in "health-related quality of life". The final outcome measurement "functional ability" showed four patients with substantial improvement at 12 months in the active treatment group and only one patient with improvement in the sham group. All these changes did not reach statistical significance in this small study population.

It was stated that after 20 patients a blinded interim analysis was planned. Based on the outcome of this interim analysis the authors concluded that there was no positive trend and found it ethically unacceptable to continue this trial. In fact, two patients from the active treatment group and three sham patients experienced more pain.

We find that this decision, to stop this study after inclusion of only 20 patients, is unacceptable for the following reasons. The conclusions are mainly based on the non-significance of *P*-values. The confidence intervals, calculated from Table 3, do include the null hypothesis but also include the hypothesis that the PIRFT group performed better with 3.5 points. Furthermore, all results show, although not statistically significant, positive results for the PIRFT group. Probably, when pooling these results with the method of O'Brien [6], the overall null hypothesis could be rejected. So, stopping the trial, because there was no trend that PIRFT is better, is unusual. Besides, the formulation of this stopping criterion is weak and should be based on a more formal criterion such as the Snappin rule [9].

An alternative explanation for stopping such an important trial could be the disappointing inclusion of the participants, i.e. only 20 of the 700 potential candidates. One can understand that a patient will be reluctant to participate when the probability of assessing the results of a sham lesion after one year is 50% (we personally would not risk this). A solution to overcome this problem is a pre-randomization design in which only the consent of the participants in the PIRFT is sought [8]. An important prerequisite is that the offered intervention is so attractive that one can expect that all patients who are offered this new, experimental, intervention will want to participate. The patients in the control group will get the standard treatment and assessments without knowing the existence of the experimental group. In this way, the control group is optimally blinded and the contrast, PIRFT versus standard treatment, is optimally realized. In addition, one could wonder whether a follow-up of one year is feasible and should be shortened to, for example, 6 months.

Insufficient power is a well-known problem in randomized clinical trials investigating the effect of interventions in patients with chronic pain. A study design such as pre-randomization might improve the inclusion of patients and prevent power problems. This pre-randomization design should be used more often in future clinical studies.

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Conflicts of interest

The authors have no conflict of interest to declare.

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