Treatment recommendations should take account of individual patient variation not just group responses

Thomas Lundeborg, Iréne Lund

Recommendations for treatment are commonly based on results evaluating variation in systematic effects (group responses) from randomised controlled trials without taking the individual patient’s variation into account. In the evaluation of acupuncture-related treatment effects, the trial design and statistical analysis used are a challenge since the assessed variables commonly have subjective properties and are based on the person’s own self-report. Thus, the results that are seen are often varied, most likely due to inter-individual variation in rating of the actual variable such that the treatment effects are expressed more (or less) in some individuals than in others. The basis for the individual variation is probably multi-modal and could be related to the individuals’ expectation, gender, genetic polymorphisms and the aetiology of the condition. The assessment methods used should preferably have proven useful in controlled trials, and the methods for statistical analysis should consider the non-metric properties of the variable and the contribution of the individuals’ variation in the results. In order to evaluate the treatment effects more properly and increase the possibility of detecting any effectiveness, it is therefore important to assess the level of perceived dysfunction or symptom, taking into account the individual variation as well as the systematic effects (the effects of the group). In the evaluation of acupuncture effects, both systematic and individual variation should be reported allowing for the detection of subgroup effects and thereby leading to treatment recommendations that are more likely to be based on each individual’s specific needs.

Acupuncture is a complex, multi-methodological treatment approach, with documented evidence in alleviation of pain and other types of subjective complaint. A complaint such as pain is a personal multidimensional experience that is defined by its different components, classified and evaluated according to aetiology, in order to provide a rational treatment approach. The evaluation of acupuncture-related effects, the trial design and the statistical analysis used constitute a challenge since the assessed variables commonly have subjective properties and are based on the person’s own self-report. Thus, the results that are seen are often varied, most probably due to interindividual variation in rating of the actual variable such that the treatment effects are expressed more (or less) in some individuals than in others. The basis for the individual variation is probably multi-modal and could be related to the individuals’ expectation, aetiology of the condition, gender and genetic polymorphisms. The assessment methods used should preferably have proven useful in controlled trials, and the methods for statistical analysis should consider the non-metric properties of the variable and the contribution of the individuals’ variation in the results. In order to evaluate the treatment effects more properly and increase the possibility of detecting any effectiveness, it is therefore important to assess the level of perceived dysfunction or symptom, taking into account the individual variation as well as the systematic effects (the effects of the group). Recommendations for treatment are commonly based on systematic effects (group responses) from randomised controlled trials without taking the patient’s individual variation into account. Another option to increase the possibility of detecting the effectiveness of treatment such as acupuncture is by using enriched enrolment randomised withdrawal trials designs. This design also allows for a naturalistic approach whereby the patient undergoes trial treatments before selecting the modality preferred, thereby optimising the effect.

Complexity of acupuncture

Acupuncture includes a number of different modes of stimulation producing varied results that have to be considered in decision-making about the use of acupuncture. In response to the different modes of acupuncture stimulation, different endogenous pain inhibitory systems have been shown to be activated. Furthermore, the function of these systems is altered depending on the aetiology of the pain, explaining why different modes of acupuncture may have different effects. From a behavioural perspective, it can be assumed that the clinical context of the acupuncture treatment may also serve as behavioural conditioning suggesting that the needling ritual per se contributes further to the therapeutic effects of acupuncture.

Assessments of the effects of acupuncture

Since there is no gold standard for assessing subjective variables like pain and other complaints, communication about the perceived effects may be optimised by using an instrument that the patient prefers. Different types of rating scales and questionnaires are commonly used for the purpose, ranging from single unidimensional scales such as the visual analogue scale, the numerical rating scale and the verbal rating scale to multidimensional and multi-item questionnaires such as the McGill pain questionnaire and the Short-Form 36-item (SF-36). The data produced are characterised as ordinal indicating that the data have an ordered structure but the magnitude of the data and the size of distances between the different categories on the scale are unknown. This means that the use of sums of, and differences between, data from rating scales are inappropriate and furthermore that such management of the data may mask valuable information of the responses of individual and of subgroups. Statistical methods for data from rating scales must take account of the rank-invariant properties of ordinal data, which means that the methods must be unaffected by the dimensions of the scale categories. Therefore, it is important to emphasise that statistical methods used for evaluation of data stemming from rating scales differ from those used for evaluation of quantitative variables since calculations such as, for example, addition or subtraction, are meaningless when applied to ordinal data.

Analysis of change in ordinal assessments in acupuncture studies

For the evaluation of change in qualitative variables, there is a preference for paired data where each individual is its own control, or other types of matched-pair data. The sign test and McNemars test may be used for analysis of change in ordinal data. For a comprehensive assessment of change in qualitative pain variables, the approach adopted by Svensson may be used.
Acupuncture and randomised controlled trials

Randomised, placebo-controlled clinical trials are recommended for evaluation of a treatment’s efficacy with the goal of separating the specific effects (verum) from the non-specific ones (placebo). Recommendations for treatment are commonly based on variation in systematic group performance. The average performance to a therapy is good in responders and poor in non-responders. Therefore poor performance in non-responders may mask the effects of a smaller subgroup of responders, and result in a false conclusion of lack of efficacy. There will be situations of great clinical need, as for example, in neuropathic pain, when acupuncture stimulation only helps a small proportion of patients. Withholding a treatment, on the basis of treatment recommendations from randomised controlled trials, which may be efficacious to some patients (the subgroup of responders) would for ethical reasons not be appropriate, emphasising the need of statistical methods and trial designs that facilitate the identification of these individuals.

Clinical acupuncture trial designs

Pain patients may have symptoms in common but the origin and the mechanism of the pain may have different aetiologies. Due to this and to differences in individual responses, including adverse effects, the effects to a therapy may vary. Therefore it has been suggested by McQuay and co-authors that we need new trial designs in order to capture the reality of the range of response in clinical practice. They have suggested that this design should have the following properties:

1. Ability to detect desirable efficacy in a subgroup.
2. Applicability when adverse effects may be problematic (particularly in non-responders).
3. Ability to cope with initial dose titration to mimic clinical practice.

These three properties are found in a trial design using enriched enrolment with randomised withdrawal (EERW). The information gathered in the pre-randomisation phase including the proportions of responders and non-responders, the optimal dose, and the number of withdrawals because of adverse effects or lack of efficacy brings additional information for defining new treatment protocols. EERW designs are suggested to be more sensitive than conventional designs that lower the proportion of responders. It has been suggested that the EERW design may be used in proof of principle studies to avoid a false conclusion of lack of efficacy, especially in chronic pain conditions where treatments neither affect a cure nor fundamentally alter the status or course of the underlying disease. It is in these conditions that acupuncture is commonly used and possibly EERW designs, naturalistic protocols and/or observational studies are better suited for the evaluation of acupuncture efficacy as compared to standard randomised controlled trials.

CONCLUSION

In the evaluation of acupuncture effects, both systematic and individual variation should be reported allowing for the detection of subgroup effects and thereby for treatment recommendations based on each individual’s specific needs. Trial designs replicating what is used in a clinical context, such as EERW and naturalistic designs, may help in identifying patients or subgroups of patients with chronic pain responding to acupuncture treatment that would not have been found if the conclusions were to be based solely on the average responses.

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