STUDIES IN ALTERNATIVE AND
COMPLEMENTARY MEDICINE
ISSN 2788-7715
JUN. 2022 VOL. 2, NO. 1

Validity of the N-of-1 Test in Assessing the Efficacy of Acupuncture

TANZAWA Shouhachi, SUZUKI Masao
Research Department of Japan Society of Acupuncture and Moxibustion

ABSTRACT

N-of-1 trials can evaluate the effectiveness of various specialized interventions in a number of patients who differ in several ways. They are easy to adopt for an exploratory study. The characteristics of the n-of-1 trial seem to be suitable for acupuncture research and the use of n-of-1 trials in acupuncture has been recommended4,13). However, the n-of-1 trial is not appropriate in cases where acupuncture treatments have long-lasting or irreversible effects. Moreover it has been pointed out that the results of n-of-1 trials cannot be easily generalized.14) Here we propose a unique protocol of n-of-1 trials that allows generalization from the results obtained from each patient attending an acupuncture clinic.

KEYWORDS

Acupuncture; AB design; N-of-1 trial; Mi-byo-chi; Clinical tvial; Asthma; Multiple randomized n-of-1 trials.

1. Introduction

In the WHO guidelines on clinical research on acupuncture, single subject experimental designs (single case design, or n-of-1 trial) are introduced4). N-of-1 trials (this term will be adopted in this paper) developed in the field of psychology, and have recently been adapted for clinical research5-9). The statistical issues concerning the evaluation of the results have been clarified10,11).

The simplest design of an n-of-1 trial is a reversal design. Baseline data are collected repeatedly during period "A" and their stability is confirmed, without treatment. Then a specific intervention is applied during period "B". The changes in outcome data are evaluated by visual inspection of a graphical figure or by the usual non-parametric test for two groups12). Repeating the two stages of the trial (A-B-A-B-A-B-) strengthens the plausibility of the results. The order BA instead of AB can be used when treatment is required urgently before the baseline period.

2. Long-Term N-of-1 Trials: A Research Design Applied in an Acupuncture Clinic

In general, the majority of patients at acupuncture clinics seem to be regular attenders who visit the clinic each time their chronic illness deteriorates. Their complaints are treated successfully by acupuncture but will

reappear after several weeks, months or years. Based on such a course of acupuncture treatment over time, we propose a new design for clinical research in acupuncture.

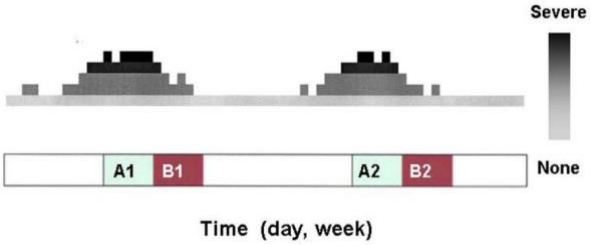

Figure 1. Hypothetical example of a long-term n-of-1 trial

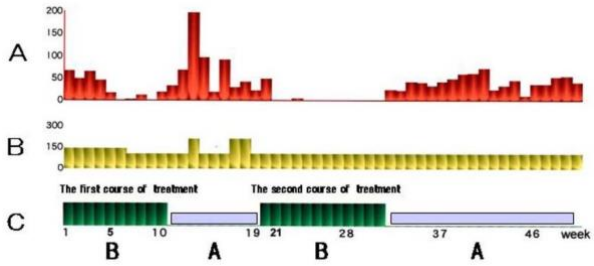

Figure 2. Example of a long-term n-of-1 trial of acupuncture

Figure 1 shows a hypothetical illustration of a longterm n-of-1 trial (ABAB design). The upper figure shows the severity of symptoms and the lower bar shows the baseline (A 1, 2) and intervention (B 1, 2) phases. In cases where patients' complaints are severe, the active intervention can be used first (BABA design). Another n-of-1 experimental design such as alternation may also be applicable. If the symptomatic changes produced by the intervention are very long lasting or permanent, a simple group comparison design should be used.

3. An Example of a Long-Term N-of-1 Trial in an Asthma Patient

The effects of acupuncture on chronic bronchial asthma were examined by n-of-1 trials (BABA design) in one patient. The patient, who was receiving care from a medical doctor but was resistant to steroid treatment (oral and by inhalation), was recruited to the study. The patient received acupuncture treatment (once a week, 10 times, repeated for a second course). Acupuncture needles (0.16 mm in diameter, 40 mm in length) were inserted and retained for 10 minutes at the following meridian points bilaterally: LI 1, CV 12, LI 5, CV 4, and B 13. The severity of asthma was recorded by a dairy of asthma symptoms, a VAS (visual analogue scale) of dyspnea, and Hugh-Jones classification. During the experiment the patient continued to receive steroids regularly.

These results show that a long-term n-of-1 trial may be useful for demonstrating the effects of acupuncture on patients over a long treatment period. This kind of situation, with repeated treatments for chronic conditions, may be very common in acupuncture clinics. So, we propose a unique protocol to allow generalization from the results obtained from long-term n-of-1 trials.

4. N-of-1 RCT (Randomized Controlled Trial)

The clinical usefulness of n-of-1 trial has become widely recognized, but, in respect of evidence based medicine (EBM) overall, its lack of external validity reduces the strength of evidence that it can contribute. In a recent EBM textbook, the n-of-1 RCT was ranked as the strongest evidence for making treatment decisions15). This

high ranking of the n-of-1 RCT is mainly based on its high internal validity, that is, the n-of 1 RCT can make it possible to decide whether an intervention is suitable for a particular subject.

The simplest n-of-1 RCT is as follows: the patient is randomly allocated to two periods of interventions, either A/B or B/A. The efficacies of interventions A and B are evaluated by the use of appropriate outcome measures, and these alternating interventions continue until a significant difference is detected between their effects. If intervention A is superior to B, then A will selected as better treatment for the subject.

Regarding the analysis of n-of-1 data, various methodological issues have been identified. Time series analysis was strongly recommended instead of conventional group comparison tests6,10). Other statistical tests such as C-statistics have also been proposed as an indicator for an n-of-1 trial11). Recent developments in computer technology make it possible to use the randomization test to analyze the data from n-of-1 trials16).

From the viewpoint of patient-oriented medicine, the n-of-1 RCT design is valuable and highly recommended. However, it should be noted that an n-of-1 RCT does not provide external validity. In Sackett's standard textbook of EMB, the n-of-1 RCT is not included in his classification of clinical trials and list of recommendations (Table 2), but he noted the importance of the design and stated guidelines for limitations on its application17). Every researcher agrees that a systematic review of homogenous RCTs is the best EBM methodology for providing external validity.

We now propose a method to increase the external validity of n-of-1 trials by adding a randomization procedure in the group comparison.

5. Multiple, Randomized N-of-1 Trials

We propose that multiple, randomized n-of-1 trials are a suitable design for increasing the external validity of a single n-of-1 study. Figure 3 shows the outline of the protocol. Patients who match the entry criteria are registered and randomly allocated into the acupuncture and control groups. Their condition or symptoms are treated by various acupuncture techniques, depending on the practitioner's method of diagnosis and treatment, the details of which should be reported in detail following the STRICTA (standards for reporting interventions in controlled trials of acupuncture) recommendations18). The effect on each patient is evaluated by a suitable statistical method such as a non-parametric test12), and then the incidence of positive and negative results is compared between the two groups using a chi-square test.

To conduct this protocol successfully, several issues should be considered. The symptom should be stable over a long period and responsive to the intervention. The severity of the major symptom or the overall condition should be recorded daily during the experimental period by simple questionnaire or VAS scale. When the symptom appears to be stable (an essential inclusion criterion), baseline data are collected (period A: days, weeks or months), then the intervention is applied repeatedly (period B: days, weeks or months). Follow-up data are also collected. The interventions should be repeated at least twice to increase the reliability of results. This protocol is easy to conduct if suitable patients can be recruited. If the sample size is large enough to allow a subgroup analysis, the effectiveness of various combinations of symptoms and methods of acupuncture treatment may also be examined by the incidence of positive or negative results.

6. The Concept of "Mi-byo-chi " for the Acupuncture Treatment

In general, the majority of patients at acupuncture clinics are regular attenders who visit to the clinic when they feel that their symptoms are getting worse, in order to restore their health. If the treatment is performed when the symptoms are not too severe, the results will be better than those obtained when the symptoms are becoming more severe. Figure 4 schematically illustrates the concept of "mi-byo-chi ".

The borderline between health and disease is not completely clear. In the ancient Chinese literature (the Yellow Emperor's textbook), the concept of mi-byo-chi was introduced. The "Mi-byo" means that the condition is pre-symptomatic, and "chi" means treatment, so the phrase indicates the importance of giving treatment before the symptoms become severe. When the treatment (thick black band) is applied to a condition that is less severe (B), the symptoms are abolished more rapidly than when it is applied to a condition that is more severe (A) (Fig. 4).

This concept clearly highlights the importance of the preventive aspect of acupuncture treatment. For evaluating the validity of the concept of "mi-byo-chi", the proposed multiple randomized n-of-1 trial may be applicable and would be worth conducting in a large sample in order to increase both internal and external validity of the clinical trial and provide stronger evidence.

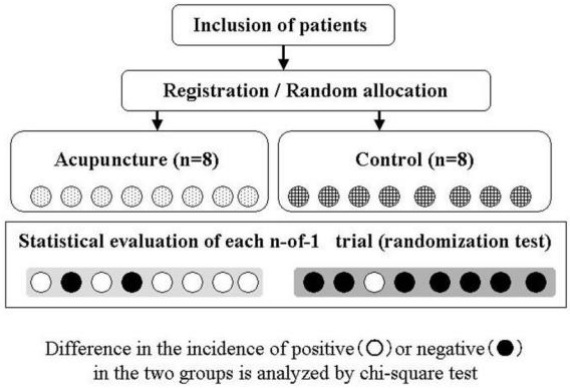

Figure 3. A block diagram of the protocol of multiple randomized n-of-1 trials

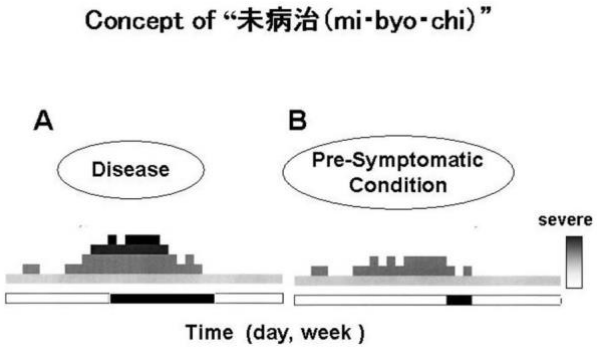

Figure 4. A schematic illustration of the concept of the "mi-byo-chi"

Patients are randomly allocated to each group then the effect of acupuncture or control intervention in each patient is evaluated by an n-of-1 trial (the randomization test can be used). Incidences of positive or negative results are analyzed statistically. (using chi-square test). In this case, chi square=6.3349 and p=0.0117. However, small samples require Yates' continuity correction, with which the results become, chi-square=4.063, p=0.0438. This result indicates the external validity of n-of-1 trials.

References

Sackett DL, Richardson WS, Rosenberg W, Haynes RB. "Evidence based Medicine." 1 st ed. Churchill Livingstone. 1998.

White A, Filshie J, Cummings TM, "Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding." Complement Ther Med 2001, 9:237-45.

Sherman KJ, Lao LX, MacPherson H et al. "Matching acupuncture clinical study designs to research questions." Clin Acupunct Orient Med. 2001, 3:12-5.

"WHO Regional Office for the Western Pacific. Guidelines for clinical research on acupuncture. WHO Regional Publications." Western Pacific Series No.15. 1995.

Guyatt GH， Keller JL， Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. "The n-of-1 randomized controlled trial: Clinic-al usefulness." Ann Intern Med. 1990, 112:293-9.

Vincent CA. "The treatment of tension headache by acupuncture: a controlled single case design with time series analysis." J Psychosom Res. 1993, 34:553-61.

Kawakita K, Okada K, Kuwata S. "Application of nof-1 trial and C statistics on acupuncture research, Proceeding of the workshop at WFAS in New York." 1996.

Guyatt G, Sackett D, Taylor DW, Chong J， Roberts R, Pugsley S. "Determining optimal therapyrandomized trials in individual patients," New Engl J Med. 1986, 314:889-92.

Mahon J, Laupacis A, Donner A, Wood T. "Randomized study of n-of-1 trials versus standard practice." BMJ. 1996, 312:1069-74.

Copyrights