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FEATURE ARTICLE

Clinical Research on Acupuncture – Concepts and Guidance on Efficacy and Effectiveness Research

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ABSTRACT Over the last few years a number of large acupuncture trials have been carried out in western countries. The following article draws on the experience from these recent large-scale trials on acupuncture to outline the way randomized trials could be used to answer questions on efficacy, effectiveness and efficiency. It will provide guidance, firstly on the underlying concepts of both efficacy and effectiveness and secondly on designing both types of trials. In addition, the controversy over specific and non-specific effects of acupuncture, emerging from the results of the above-mentioned trials, will be highlighted. Suggestions for future clinical research on acupuncture include: greater reflection on the complex approach of Chinese medicine, and transparent and detailed reporting according to CONSORT and STRICTA guidelines. The current data on acupuncture point-specific effects do indeed have relevance, however for valid decision-making on acupuncture, further clinical trials on effectiveness and cost-effectiveness are required to provide realistic benefit estimates for future health care.

KEYWORDS acupuncture, efficacy, effectiveness, randomized controlled trial, randomized pragmatic trial

All interventions which are part of health care provided by health insurances, including acupuncture, should have a solid evidence base. Results from randomized controlled trials (RCTs) are considered, within the hierarchy for single studies, to have the highest level of evidence. The results from RCTs are summarized in systematic reviews and meta-analyses, which are often used to inform policy makers for decision making on whether interventions for particular conditions are covered by state funds or insurance-based reimbursement.

Patients frequently choose acupuncture treatment[1-3] though there is no clear evidence for acupuncture point-specific effects. However, there is a real shortage of data on the effectiveness of acupuncture in routine medical care. In 2000, the German Federal Committee of Physicians and Health Insurers proposed that large research initiatives on acupuncture could be conducted by health insurance companies for several pain syndromes[4]. For one of these research initiatives, we designed a model project with the aim of evaluating efficacy, effectiveness, safety and costs of acupuncture treatment in patients with one of the following chronic pain syndromes: osteoarthritis of the knee or hip, low back pain, neck pain or headache.

The following article draws on the experience from the recent large-scale trials on acupuncture to outline the way randomized trials can be used to answer questions on efficacy, effectiveness and efficiency of acupuncture for pain syndromes. In addition, the controversy around specific and non-specific effects of acupuncture will be highlighted and suggestions for future clinical research will be addressed.

The Challenge of Whole Medical Systems

Acupuncture is a component of Chinese medicine, a whole medical system using a unique diagnostic and therapeutic approach. In clinical practice, the treatment is usually tailored to the individual patient, whereas in clinical trials it is mainly applied in a standardized manner to all patients. For this reason clinical research on whole medical systems faces two major disadvantages[5]: (1) a

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fragmentation of their treatment and (2) interventions which follow a Western diagnostic approach. This should be taken into account when discussing the evidence on acupuncture.

The Concepts of Efficacy and Effectiveness in Clinical Research

A clinical study can focus more on the efficacy or more on the effectiveness of acupuncture treatment. The difference between the terms efficacy and effectiveness do not appear to be well understood and there seems to be a grey area in the understanding of the different aims of efficacy and effectiveness studies[5]. "Efficacy" refers to "the extent to which a specific intervention is beneficial under ideal conditions"[6]. It concentrates primarily on the causal effects of a treatment e.g. by comparing an intervention to a placebo. "Effectiveness" is a "measure of the extent to which an intervention, when deployed in the field in routine circumstances, does what it is intended to do for a specific population"[6]. In other words "effectiveness" reflects whether a treatment is beneficial under conditions close to routine care and such effectiveness studies use a more "pragmatic" approach.

Although efficacy studies (which include a placebo control) are mainly used for decision making, it is obvious that there is a need for more evidence from comparative effectiveness research (CER)[7]. Although the aspects of effectiveness research are not new[8], the terminology and the suggestions for future research are not straightforward. CER is a heterogeneous field and can include single interventions (e.g. acupuncture) or complex interventions (e.g. whole medical systems such as Chinese medicine). Depending on the research question, different study designs can play a role, which may include registries, observational studies, comparative studies and randomized trials. Randomized trials in routine care are often referred to as pragmatic trials[9]. Pragmatic trials are designed to find out how effective a treatment really is in everyday practice and their purpose is to allow informed decisions to be made about routine practice. Guidelines have been designed to improve the reporting of pragmatic trials[10] and for this purpose an indicator tool was developed for randomized trials to assess the grade of effectiveness represented in randomized trials[11]. Evidence on effectiveness can provide information on clinical practice. However, if one wants to isolate the acupuncture point-specific effect in randomized studies, the efficacy of acupuncture compared to sham acupuncture is required. There are some main differences between efficacy and effectiveness studies[10] (see Figure 1).

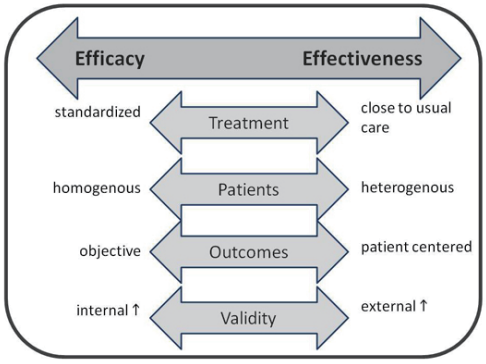

Figure 1. Characteristics of Randomized Efficacy and Effectiveness Studies

Since efficacy studies in acupuncture research evaluate if it works under ideal conditions, a homogenous patient population is included. Non-compliant participants and those with conditions which might dilute the effect are often excluded from the study. The acupuncture protocol is standardized, the compliance is monitored closely and objective or surrogate parameters are mainly used to measure the treatment success. Effectiveness studies look at whether acupuncture works when used in routine care. There is less pre-selection of the patients, often resulting in substantial heterogeneity, representative of the population under investigation. Furthermore, the treatment protocol is close to routine care and patient-centred outcomes are used to determine the effectiveness. It must be taken into account, when planning such effectiveness trials, that due to increased heterogeneity in the baseline characteristics and in the treatment protocol, a larger sample might be needed to detect a statistically significant difference between the groups. The advantage of pragmatic trials is that they can compare complete treatment systems (e.g. a complex Chinese medicine intervention versus a complex conventional intervention for osteoarthritis of the knee) and that they can be combined with health economic evaluations to determine the cost-effectiveness of the intervention compared to the control.

Results from Large German Studies on Efficacy and Effectiveness of Acupuncture

A significant number of acupuncture studies have been published over the last few years. Our large-scale trials from Germany will be introduced in order to help understand the gap between efficacy and effectiveness for acupuncture treatment of chronic pain. These studies were initiated by the German statutory health insurance companies[4] and covered both aspects: acupuncture point-specific effects (efficacy) and the overall effect of an additional acupuncture treatment (effectiveness). The effectiveness of additional acupuncture treatment was evaluated in pragmatic randomized studies for four different diagnoses: osteoarthritis of the knee or hip[12], low back pain[13], neck pain[14], or headache[15]. In these Acupuncture in Routine Care (ARC) studies patients in the acupuncture group received acupuncture[10-15] sessions within three months, whereas patients in the control group did not receive acupuncture within the same three months. All patients were allowed to use routine medical care. Within these same studies the cost-effectiveness was determined using a social perspective, based on quality adjusted life years and health insurance company data, from the same sample population[13,16-18]. The main results of these studies showed that additional acupuncture treatment was more effective than routine care alone. In addition, acupuncture complementary to routine care appears to have acceptable cost-effectiveness.

Four further studies focusing on the efficacy of acupuncture were carried out at the same time: comparing acupuncture with a superficial penetrating sham control at non acupuncture points in patients with the following pain syndromes: osteoarthritis of the knee[19], chronic low back pain[20], migraine[21], and tension-type headache[22]. In these single-blind Acupuncture Randomized Trials (ART), both groups received a total of 12 treatments over a period of two months. For three of the four diagnoses, it was not possible to determine a general acupuncture point-specific effect. A significant difference between acupuncture and sham acupuncture could only be shown for osteoarthritis of the knee[19]. For chronic low back pain, migraine and tension-type headache, the effect in the penetrating sham acupuncture group appeared to be comparable to that in the acupuncture

Table 1. Results from the Acupuncture Randomized Trials and the Acupuncture in Routine Care Studies

Diagnosis	N	Intervention (ACU)	Control (CON)	Treatment dose	Results
Chronic low back pain					
Brinkhaus, et al 2006[20]	147/75	semi-standardized acupuncture with manual stimulation	penetrating sham, no stimulation	12 sessions over 2 months	*P*=0.260 SMD =0.15
Witt et al 2006[13]	1451/1390	non standardized acupuncture and usual care	usual care only	10-15 sessions over 3 months	*P*<0.001 SMD=0.41 ICER=10526€
Chronic neck pain					
Witt, et al 2006[14]	1753/1698	non standardized acupuncture and usual care	usual care only	10-15 sessions over 3 months	*P*<0.001 SMD=0.64 ICER=12469€
Migraine					
Linde, et al 2005[21]	145/81	semi-standardized acupuncture with manual stimulation	penetrating sham, no stimulation	12 sessions over 2 months	*P*=0.960 SMD=0.06
Jena, et al 2008*[15]	877/838	non standardized acupuncture and usual care	usual care only	10-15 sessions over 3 months	*P*<0.001 SMD=0.46 ICER=5050€
Tension type headache					
Melchart, et al 2005[22]	132/63	semi-standardized acupuncture with manual stimulation	penetrating sham, no stimulation	12 sessions over 2 months	*P*=0.580 SMD=0.11
Jena, et al 2008*[15]	629/636	non standardized acupuncture and usual care	usual care only	10-15 sessions over 3 months	*P*<0.001 SMD=0.48 ICER=4800€
Osteoarthritis of the knee					
Witt, et al 2005[19]	149/75	semi-standardized acupuncture with manual stimulation	penetrating sham, no stimulation	12 sessions over 2 months	*P*<0.001 SMD=0.18
Witt, et al 2006[12]	175/167	non standardized acupuncture and usual care	usual care only	10-15 sessions over 3 months	*P*<0.001 SMD=0.72 ICER=20711€

*evaluated within the same ARC study, SMD=standard mean difference (effect size: small <0.3, moderate 0.3-0.8, large >0.8), ICER= incremental cost-effectiveness ratio

group. For more information on the ART and ARC studies, see Table 1. One of the main advantages of the whole project was the fact that both study types ART and ARC complemented each other in content and method. ART focused on determining - with high internal validity - the specific efficacy of acupuncture. The aim of ARC, on the other hand, was to evaluate - with high external validity - the effectiveness of acupuncture in routine medical care. When comparing the size of the effect between the acupuncture and control groups for both the efficacy (ART) and effectiveness studies (ARC), the overall effect of acupuncture between additional acupuncture and routine care only, was much larger than between acupuncture and sham acupuncture (see Figure 2).

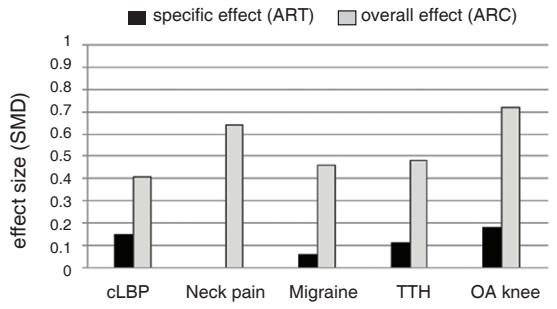

Figure 2. The Effect Size in the Differences between Acupuncture and Control Groups (standard mean differences, SMD; small <0.3, moderate 0.3-0.8, large >0.8)

Notes: ART difference acupuncture *vs.* penetrating sham control, ARC difference acupuncture in addition to routine care *vs.* routine care only; cLBP = chronic low back pain, TTH= tession type headache, OA knee=osteoarthritis of the knee

Although for osteoarthritis of the knee, the difference was statistically significant between acupuncture and the penetrating sham control group, the size of the acupuncture point-specific effect was small (SMD 0.18), whereas for all diagnoses the overall effect of acupuncture as an add-on to routine care was of moderate size (SMD 0.41-0.72). While the effectiveness of additional acupuncture treatment was proven, the evidence for acupuncture point-specific effects was lacking.

The Efficacy and Effectiveness Gap in Clinical Acupuncture Research

The results have not been what the acupuncture profession had expected[23] and acupuncturists and methodologists are still involved in complex ongoing discussions. Based on our and other recent studies, there is a continuing debate regarding the role of the placebo effect in acupuncture. The most recent acupuncture trial on chronic low back pain[24] found that even non-penetrating sham acupuncture, stimulated with a toothpick at the acupuncture points, was as effective as real acupuncture. The simplest explanation, as evaluated in effectiveness studies, is that the clinically relevant benefits from acupuncture as a whole, are mostly attributable to non-specific factors such as patient expectations and patient-practitioner interaction; and that the acupuncture point-specific effect determined in sham controlled studies is marginal compared to the total effect (see Figure 2). This is strongly supported by evidence from acupuncture studies carried out in the West and even in those diagnoses where Meta-analyses determined a significant difference between acupuncture and sham acupuncture, the size of the effect between both groups was small and clinically irrelevant[25,26]. However, it has been shown that the effects of sham acupuncture when compared with a no treatment control are moderate (SMD 0,45)[27]. It seems that sham acupuncture interventions are often associated with moderately large non-specific effects. This could make it more difficult to detect small additional specific effects. The meta-analysis by Linde et al suggests that sham acupuncture interventions might be associated with larger effects than pharmacological and other physical placebos[28]. They also found that the effects of acupuncture interventions including both specific and non-specific effects, often seem to be at least moderate in size.

In sham controlled trials we can distinguish between penetrating sham controls and non-penetrating sham controls. When compared with a non-penetrating sham control, the effect of a penetrating sham control includes two aspects: the acupuncture point-specific effect and the physiological effects due to skin penetration (see Figure 3). One would, therefore, expect the difference between acupuncture and sham acupuncture to be larger for a non-penetrating than a penetrating sham control. However according to the recent meta-analysis, despite limited available data, skin penetration or no skin penetration does not seem to make a big difference[28]. Nevertheless, we must keep in mind that each of these control types answers slightly different research questions. The use of a non-penetrating sham control does not answer the question

Chin J Integr Med 2011 Mar;17(3):166-172

whether needling at the right acupuncture points is necessary. This question can only be answered by a penetrating sham control.

The effect size in effectiveness trials depends largely on the kind of control group. If for example, the control receives routine care only, whereas the acupuncture group receives acupuncture in addition to routine care, the effect is expected to be at least moderate or large, because the measured effect includes all non-specific effects of the treatment (Figure 3).

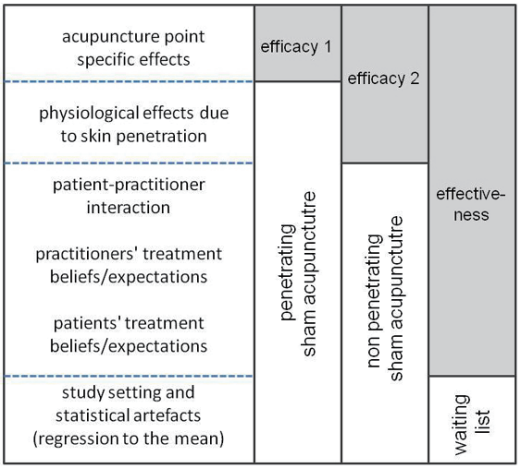

Figure 3. Components of the Patients' Benefit and Aspects of Efficacy and Effectiveness

If a standard treatment control group is used, the difference compared to acupuncture would be expected to be smaller than for a routine care control, because standard care is expected to be more effective than routine care. The studies used as an example here were performed within a Western cultural background and use different treatment strategies than studies from China (incl. acupuncture points, type of stimulation, frequency, etc.), which could influence the outcome[29].

These examples show that it is important to obtain detailed information about the intervention and the control groups from the publications, to allow for informed conclusions on the results.

Reporting Clinical Research on Acupuncture

The CONSORT statement is an evidence-based, minimum set of recommendations for reporting RCTs[30] and the STRICTA extension[31] for acupuncture studies provides clear and detailed guidance on reporting acupuncture interventions. To allow transparent reporting the STRICTA checklist includes details on: the acupuncture rational, needling, treatment regimen, other interventions in the acupuncture group (e.g. moxibustion) or the setting, practitioner background and detailed information about the control group.

What Evidence Is Needed for the Integration of Acupuncture into the Healthcare System in the West?

In most Western countries an evidence base is required to justify the integration and the reimbursement of treatments. The main question arising from the efficacy effectiveness gap on acupuncture is: What do we want to pay for? At first glance this seems obvious: evidence-based acupuncture treatment for a given condition. However, what kind of evidence will play the leading role – the evidence on the specific effect or the overall evidence of the whole treatment approach? This brings us to the core point: when discussing the results of efficacy or effectiveness, their relevance for decision making has to be clarified. This discussion focuses on the question whether the evidence for the specific effect has to be shown before the evidence that it works in routine care becomes relevant. This approach would follow the systematic steps used in clinical drug research (phase Ⅰ-Ⅳ). Acupuncture has existed much longer than these systematic research strategies and for those traditional treatments which are already implemented in the healthcare system, the opposite approach is suggested[32]. This includes the following five phases: (1) Context, paradigms, philosophical understanding and utilization; (2) Safety status; (3) Comparative effectiveness; (4) Component efficacy and (5) Biological mechanisms.

However, the relevance of efficacy and effectiveness data is not only a methodological discussion, but also an ethical and political discussion[5].

The evidence surrounding the placebo effect and its clinical relevance has been an emerging topic over the last few decades. From an ethical point of view it is difficult to provide patients with a treatment, which has not shown specific effects, without informing them of this fact[33]. However, within this context it might make sense to differentiate between pharmacological treatments and non-pharmacological treatments.

Acupuncture is a non-pharmacological treatment where the patient-practitioner interaction, including touching the patient when inserting and stimulating the needles, is an inseparable part of the acupuncture treatment. Focusing only on point specificity from sham controlled trials, involves separating a complex intervention into different aspects and drawing conclusions on only one part of a complex intervention. The overall effect from acupuncture having relevance for patient care is supported by the recent paper on clinical expertise for acupuncture on chronic low back pain published in the New England Journal of Medicine[34]. In this paper it was concluded that although there is negative evidence on the acupuncture point-specific effects, acupuncture could be given to patients with uncomplicated low back pain, who have not responded to conventional treatments and who request acupuncture.

Suggestions for Future Research

Most of the previous research on acupuncture has followed the principles of conventional drug research by testing the superiority of a more or less standardized treatment protocol over a sham control for a clearly defined conventional diagnosis. Although more evidence on the validity and reproducibility of Chinese pattern diagnoses is still needed, future studies should include Chinese pattern diagnoses to (1) evaluate the influence of the pattern diagnoses on the treatment response and 2) to allow a more individualized treatment protocol. Chinese medicine, as a whole medical system, includes not only acupuncture but also diet, pharmacotherapy, Qigong and Tuina. More studies are needed which compare the complex approach of Chinese medicine with complex conventional care.

The differentiation between efficacy and effectiveness does sometimes seem difficult and this is not only due to wrongly used terminology, but also due to a grey area between both terms. Due to this it is strongly advised to have very transparent and detailed reporting, not only on the inclusion and exclusion criteria of the patients, but also on the intervention, which should follow the STRICTA guidelines[31]. However, the same details have to be provided for the control group, including clear information on the kind of routine care or standard care provided for the patients. For a meaningful allocation of resources within the healthcare system, cost-effectiveness studies will play a more prominent role in the future and could be part of comparative effectiveness research.

Conclusion

More evidence on efficacy, effectiveness and cost-effectiveness is needed from acupuncture research to inform decision makers on the integration of acupuncture into healthcare systems. In addition, more insights into the mechanisms of acupuncture for the relevant diagnosis would be beneficial. Data on acupuncture point-specific effects does have relevance, however for valid decision making on acupuncture, further clinical trials are needed, which reflect the situation in routine care to provide realistic benefit estimates for future healthcare.

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