

Physiological basis of therapeutic effects of sham acupuncture in recent clinical trials

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Abstract

Recent well-designed large scale RCTs of acupuncture on osteoarthritis of the knee, chronic low back pain and other musculoskeletal pain symptoms have clearly demonstrated that real acupuncture intervention actually work and their meta-analysis also confirmed that acupuncture therapy are more effective than conventional and/or usual care. But there were no significant difference between real and so-called sham acupuncture. These results tend to lead a conclusion that acupuncture has no specific effect but it has strong placebo or expectation effect, although both acupuncture interventions produced much greater clinical effects than conventional cares.

From physiological view points, sham acupuncture interventions such as minimal acupuncture, Streitberger or Park sham needle used in the clinical trials seem to be not inert intervention. Several sensory receptors could be excited by these interventions. It should be noted that the response characteristics of polymodal receptors, which were assumed to be a possible sensory candidate for both acupuncture and moxibustion, are in accordance with the candidate which activated by such sham interventions. So the actual clinical effect of so-called sham acupuncture intervention should be clarified by comparison with another type of inert sham/placebo acupuncture.

A RCT conducted in Japan using press tack needle (PTN), thin and short (0.18 mm in diameter, 0.6 mm in length) needle attached to a plastic plate and its placebo one (only small metal ball attached instead of fine short needle) were used to clarify a specific effect of real PTN

The main outcome measure was pain in VAS scale before and after triathlon race. Blinding of two types of PTN to the subjects was also performed and the subjects could not discriminate real and sham PTN. Analgesic effects of real PTN were significantly much higher than the sham PTN. Moreover, recently Korean group examined the skin temperature of the knee in OA patients and found that real PTN produced a significantly much higher skin temperature increase by real PTN than that of sham PTN, and masking to both PTN was sufficient.

These results clearly demonstrated that clinical benefits of acupuncture have been well established, but its specific effects should be confirmed by further studies using more reasonable sham devices.

I. Introduction

Recent clinical trials of acupuncture on osteoarthritis of the knee and other musculoskeletal pain symptoms have clearly demonstrated that real acupuncture treatments are significantly more effective than conventional and/or usual care¹⁻⁵⁾, and their meta-analysis also confirmed the efficacy of acupuncture treatment⁶⁻⁷⁾. A series

of large scale clinical trials with high quality were conducted in German, and minimal acupuncture was used as sham intervention which characterized by shallow needling to non acupuncture points without de-qi sensation⁸⁾. Figure 1 shows two typical results of German trials, and there were no statistical significant differences between the real and sham acupuncture groups. The minimal acupuncture was assumed as inert intervention, and these

results tend to lead a conclusion that acupuncture has no specific effect but it has strong placebo or expectation effect, although both real and sham acupuncture treatment produced statistically significant much stronger effects than conventional/ standardized therapies.

There are several issues still remain to be clarified for concluding the lack of specific effects of acupuncture. If the sham interventions used in these acupuncture trials had some physiological effects, the conclusion might be different, and the results should be re-considered as the results of comparison of two different acupuncture procedures.

From physiological points of view, minimal acupuncture which penetrates the skin is difficult to assume as inert intervention. Several other sham acupuncture devices have been developed. Typical ones were developed by Streitberger⁹⁾, Park¹⁰⁾ and Takakura¹¹⁾. The tip of needle was blunt and the needle shaft was withdrawn into the needle grip. When the sham device was tried to insert the needle tip presses the skin and the needle seems to be inserted into the deep tissues visually. These sham devices seems to be more reasonable for sham acupuncture, and several clinical trials have been conducted using these sham device¹²⁾. So it is important issue to examine these sham devices are physiologically inert or not.

In the present study, physiological potential of so-called sham acupuncture intervention was examined by microneurogram technique focusing on the neural activity of polymodal receptors. Another type of acupuncture and its sham/placebo called press tuck needle (PTN) was introduced and several results of basic and clinical studies were briefly introduced as a possible device of future acupuncture research.

Responses of the polymodal receptors to sham acupuncture stimulation

Two young healthy subjects who gave written informed consent were used. The subject sat on the on bed with side down position, and single unit discharges were recorded from the peroneal nerve at the low leg with microneurography technique with a fine insulated needle (Frederick Hair 10 μ m, 180 μ m, tungsten). The response characteristics of the recorded unitary discharges to mechanical and thermal stimulation applied to the receptive field, and its conduction velocity were measured and identified as C polymodal-type receptor. The responsiveness of CMH (C mechano-heat) units to real PTN, sham PTN and pressure with blunt needle (sham acupuncture) were examined.

Figure 2 demonstrates that a CMH unit responded to real PTN transiently and no discharges were elicited by

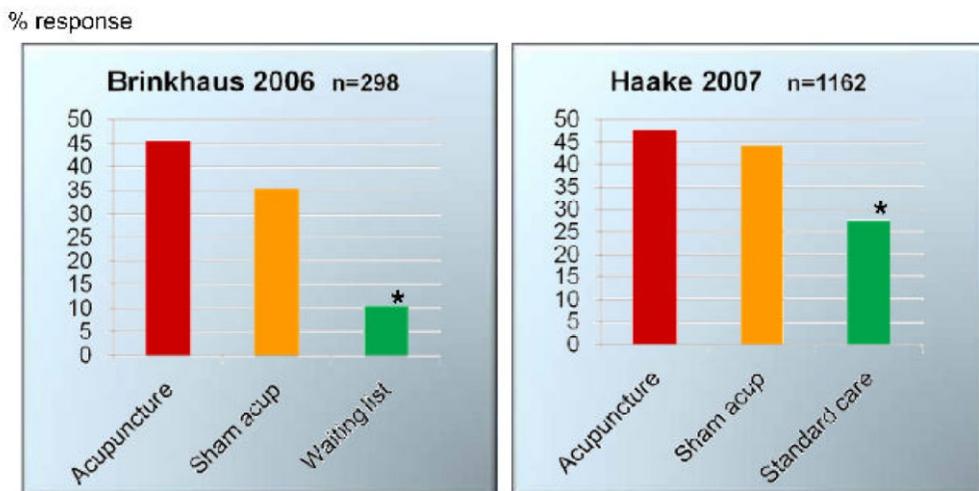


Figure 1. Typical examples of clinical data of acupuncture, sham and waiting list, or standard care on the patients of low back pain.

sham PTN application, however a phasic weak response was observed when the attached tape was removed. On the other hand, application of pressure with a blunt needle tip also activated the CMH, but this unit did not respond to tactile stimulation.

The majority of CMH units of the skin are considered

as polymodal receptor. The response characteristics of the polymodal receptors, which were assumed to be a possible candidate for both acupuncture and moxibustion, are in accordance with the candidate, so it should be pointed out the fact that non-penetration sham acupuncture can activate the polymodal receptors of the skin.

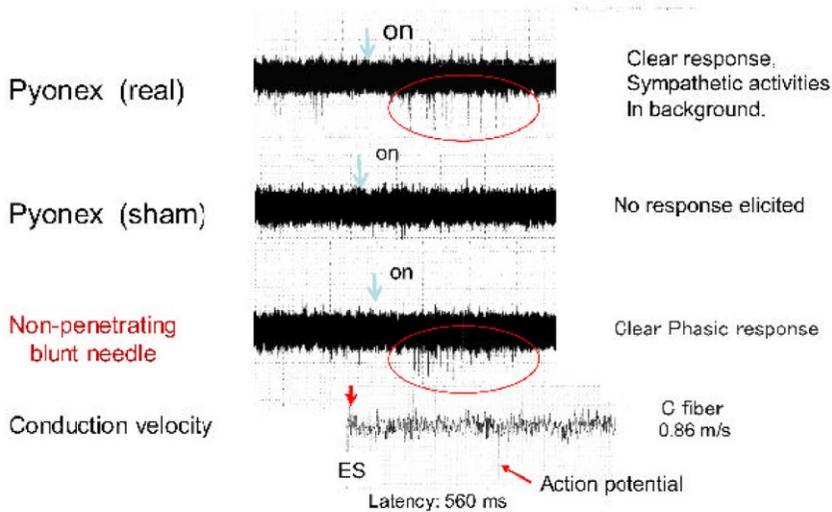


Figure 2. Example of neural responses of a C mechano-heat receptor to PTN and its sham and non-penetrating acupuncture stimuli.

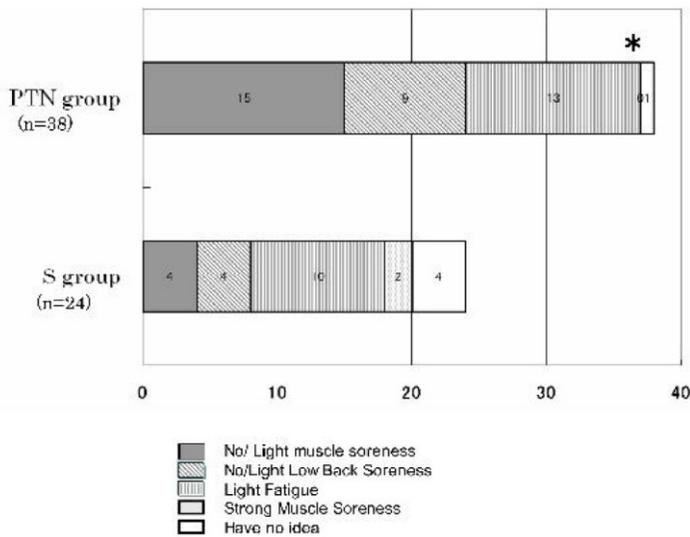


Figure 3. Effects of real PTN and its sham on muscle symptoms in triathlon athlete.

Effects of press tuck needle on the muscle soreness after the triathlon race.

The first RCT of PTN was conducted on the athletes of triathlon race¹³. The subjects were participants of a triathlon race (n=62), they were randomly allocated to real and sham PTN. Ten PTNs were attached on the low back skin bilaterally. Subjects were asked to answer the questionnaire before, immediately after and 24 hours after the race. Figure 3 indicates the results of PTN or sham PTN attached groups at 24 h after the race. A significantly higher pain relief was obtained by real sham than those of sham control. And a survey on the masking of real and sham PTN was also conducted. The results clearly demonstrated that the subjects could not discriminate the real and sham PTN precisely (p<0.05)

Effects of real and sham PTN on skin temperature

Physiological effects of PTN were also examined using healthy volunteers (n=12). Real PTN and sham PTN were attached to the skin around the knee joint and the changes of skin temperature around the joints were measured by themography before and after the PTN attachment. It is demonstrated that the real PTN produced a significantly higher skin temperature than sham

PTN. Masking of the real and sham PTN was also successfully performed. (unpublished data by Kim YS).

Increase of the skin temperature by real PTN suggest that it induces axon reflex which mediated by C afferent fiber receptors.

Discussion

Various control interventions such as minimal acupuncture or sham acu-punctures have been used in recent clinical trials of acupuncture, and they induced similar efficacy to those obtained by real Chinese style acupuncture treatment, which requires "de-qi" sensation by manipulation of needle, and no significant difference between real and sham acupuncture groups were detected.

In the present electrophysiological study, it is clearly demonstrated that the sham interventions such as minimal acupuncture and non-penetrated sham acupuncture could activate the polymodal-type C fiber receptors in the skin, The polymodal-type receptors have been proposed as a candidate of acupuncture and moxibustion stimulation¹⁴. Other somatosensory receptors such as touch and pressure receptors were also excited by non-penetrating sham acupuncture¹⁵, but they have no sensi-

Table 1. Summary of characteristics of polymodal receptors and their relations to acupuncture and moxibustion stimuli and acupuncture/ trigger points.

	Polymodal Receptors	Acupuncture & Moxibustion	Acupuncture/Trigger points
Modality	Nociceptor, low threshold	Noxious but not painful	Tenderness
Responsiveness	Mechanical, thermal, chemical stimuli	Acp: Mechanical, chemical stimuli, Mox: thermal, chemical stimuli	Highly sensitive region
Sensitization	Easily sensitized	Produce sensitizing substances	Existence of sensitized nociceptors
Sensory Events	Evoke deep pain "de-qi"	Evoke "de-qi" sensation	Sensitive region for "de-qi"
Axon Reflex	Possible candidate	Evoke axon reflex	Sensitive region for axon reflex
Morphology	Free nerve endings		No particular structures
Distribution	Whole body, various tissues		Whole body, various tissues

tivity to heat stimulus and their roles in acupuncture action mechanism might be less important than the polymodal-type receptors.

Polymodal receptors are responsive to mechanical, thermal and chemical stimuli, which respond to pain substances and sensitizing chemicals such as bradykinin and prostaglandins. It is well known that they are activated by both acupuncture and moxibustion. The response characteristics of the polymodal receptors and their functional and morphological similarities to acupuncture/tender points were summarized in Table 1. They offer a rational explanation to the issues of mysterious acupuncture points. In the long history of acupuncture and moxibustion, it is now clearly demonstrated that moxibustion therapy was older than acupuncture, and the concept of meridians might be borne from the clinical experiences by moxibustion not by acupuncture.¹⁶⁾ So, touch and pressure receptors, which did not respond to thermal stimuli, could be excluded in the peripheral action mechanism of acupuncture and moxibustion theoretically.

In comparison with sham PTN, the real PTN could activate the polymodal type receptor, and produces significantly stronger clinical efficacy on pain relief and skin temperature increment. The masking of real and sham PTN were succeeded in both studies. Moreover, the PTN seems to be much safer than those of penetration-type real acupuncture as its shaft of needle is only 0.6 mm.

These results strongly suggest the usefulness of the real and sham PTN in future clinical trials to clarify the specific effects of acupuncture therapy.

References

- 1) Berman BM, Lao L, Langenberg P, Lee WL, Gilpin AM, Hochberg MC. Effectiveness of acupuncture as adjunctive therapy in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med.* 2004; 141 (12): 901-10.
- 2) Witt C, Brinkhaus B, Jena S, Linde K, Streng A, Wagenpfeil S et al. Acupuncture in patients with osteoarthritis of the knee: a randomised trial. *Lancet* 2005; 366(9480): 136-43.
- 3) Scharf HP, Mansmann U, Streitberger K, Witte S, Kramer J, Maier C et al. Acupuncture and knee osteoarthritis - a three-armed randomized trial. *Ann Intern Med* 2006; 145(1): 12-20.
- 4) Brinkhaus B, Witt CM, Jena S, Linde K, Streng A, Wagenpfeil S et al. Acupuncture in patients with chronic low back pain: a randomized controlled trial. *Arch Intern Med* 2006; 166(4): 450-7.
- 5) Haake M, Muller HH, Schade-Brittinger C, Basler HD, Schafer H, Maier C et al. German Acupuncture Trials (GERAC) for chronic low back pain: randomized, multicenter, blinded, parallel-group trial with 3 groups. *Arch Intern Med* 2007; 167(17): 1892-8.
- 6) White A, Foster NE, Cummings M, Barlas P. Acupuncture treatment for chronic knee pain: a systematic review. *Rheumatology (Oxford)* 2007; 46(3): 384-90.
- 7) Manheimer E, White A, Berman B, Forsy K, Ernst E. Meta-analysis: acupuncture for low back pain. *Ann Intern Med.* 2005; 142(8): 651-63.
- 8) Vincent CA. A controlled trial of the treatment of migraine by acupuncture. *Clin J Pain.* 1989; 5(4): 305-12.
- 9) Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *Lancet* 1998; 352: 364-5.
- 10) Park J, White A, Stevinson C, Ernst E, James M. Validating a new non-penetrating sham acupuncture device: two randomised controlled trials. *Acupunct Med* 2002; 20(4): 168-74.
- 11) Takakura N, Yajima H. A double-blind placebo needle for acupuncture research. *BMC Complement Altern Med* 2007; 7: 31.
- 12) Vas J, Mendez C, Perea-Milla E, Vega E, Panadero MD, Leon JM, Borge MA, Gaspar O, Sanchez-Rodriguez F, Aguilar I, Jurado R. Acupuncture as a complementary therapy to the pharmacological treatment of osteoarthritis of the knee: randomised controlled trial. *Br Med J.* 2004; 329 (7476): 1216.
- 13) Kaneko Y, Furuya E, Akamoto A. The effects of press tack needle treatment on muscle soreness after triathlon race -sham-controlled study *JAM* 2009; 6: 22-30.
- 14) Kawakita K. and Gotoh K. Role of polymodal receptors in the acupuncture-mediated endogenous pain inhibitory systems. In: Kumazawa et al. eds., *Progress in Brain Research* Vol.113, The polymodal receptor, Elsevier Science BV, 1996, pp 507-523.
- 15) Kagitani F, Uchida S, Hotta H, Aikawa Y. Manual acupuncture needle stimulation of the rat hindlimb activates groups I, II, III and IV single afferent nerve fibers in the dorsal spinal roots. *Jpn J Physiol.* 2005; 55(3): 149-55.

- 16) Harper D. Early Chinese Medical Literature. The Mawangdui medical manuscripts. 1 st ed. London: Kegan Paul International, 1998.