



Short communication

Effect of placebo acupuncture over no-treatment: A simple model incorporating the placebo and nocebo effects

Yun Hyung Koog^{a,b,*}^a Honam Research Center, Medifarm Hospital, Suncheon, South Korea^b Department of Oriental Medicine, Medifarm Hospital, Suncheon, South Korea

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ABSTRACT

Conventionally in controlled trials of drugs or modalities, the placebo and nocebo effects have been determined separately and understood to be the difference between the placebo and no-treatment groups. Recently, the effect of placebo acupuncture over no-treatment was found to be associated with the placebo and nocebo effects together. If these two effects are inseparable in acupuncture treatment, the conventional method of determining placebo and nocebo effects at the trial level will not reflect pure placebo or nocebo effects. Furthermore, if these effects are inseparable, observations about the efficacy of acupuncture will be biased when considering only the placebo effect. A simple mathematical model incorporating both the placebo and nocebo effects will be provided to see how the efficacy of acupuncture is affected.

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1. Background

Although placebo and nocebo effects have been acknowledged for decades, their definitions have not been firmly established.¹ Even in placebo-controlled trials in which non-specific effects can be assumed to be caused by placebos, defining these effects logically is challenging.² Previously, placebo and nocebo effects had been understood to indicate improving or worsening of symptoms that occurred during treatment with placebo drugs or modalities. However, such usage of the terminology did not necessarily reflect the 'true' placebo or nocebo effects, because improving or worsening of symptoms may be related to a number of factors (e.g., natural course of the disease, spontaneous remission, regression of the mean). In order to control for noise in determining the placebo and nocebo effects, both placebo and no-treatment groups are needed.³ There is now agreement that these two effects indicate the differences in positive or negative outcomes between the placebo and no-treatment groups in a trial.^{4,5}

On the basis of this consensus, a series of studies have investigated placebo and nocebo effects in acupuncture.^{6–11} One earlier study reported by Madsen et al.⁶ analyzed data from 13 pain trials that included placebo acupuncture and no-treatment groups and found the placebo effect to be 0.42 (95% CI: 0.23–0.60) in stan-

dardized mean difference. Although this magnitude was clinically relevant, the study by Madsen et al.⁶ concluded without clear evidence that the placebo effect was subject to biases (e.g., insufficient blinding, reporting bias).

Similarly, a study conducted by Linde et al.⁷ analyzed data from 37 acupuncture trials and showed the placebo effect to be similar in magnitude to that of the study by Madsen et al.⁶ It also found that the efficacy of acupuncture pooled across trials may be subject to a small study effect (i.e., a bias in which smaller trials show larger treatment effects) that was not evident for the placebo effect. The authors did not study this association but acknowledged it, simply stating that "it is difficult to assess to what extent and in which direction biases can distort the placebo effect."⁷

Koog et al.⁸ confirmed findings of the study by Linde et al.⁷ similarly showing that, in pooled-data analysis of all acupuncture trials, the efficacy of acupuncture – but not the placebo effect of acupuncture – was subject to a small study effect. In further analyses, publication bias – in which reports of small trials with negative results would less likely be published in journals – was found to be a source of the small study effect. Surprisingly, the placebo effect adjusted for this bias was greater than the placebo effect from trials that were currently available.

In a subsequent study presented by We et al.⁹ the placebo effect of acupuncture was found not to be influenced by any trial or patient characteristics, except for publication year. In trials published more recently, the placebo effect increased by 0.05 in standardized mean difference per year. In fact, all factors considered primary were investigated in earlier studies^{6–8} and none was

* Correspondence to: Honam Research Center, Medifarm Hospital, Suncheon, South Korea. Tel.: +82 61 729 3300; fax: +82 61 729 3301.

E-mail address: samlungchim@hanmail.net

associated with the placebo effect. Therefore, the finding of a linear relationship between the placebo effect and the publication year is unexpected. Again, this finding supports the possibility of publication bias. If findings from earlier trials showing positive treatment effects of acupuncture were published in journals, it might be reasonable to expect the placebo effect in those trials to be relatively smaller. Indeed, it has become more difficult in recent trials to show superiority of acupuncture over placebo acupuncture, thus making some researchers believe that acupuncture is a placebo treatment.¹²

Finally, a study completed by Koog et al.¹⁰ examined the placebo effect from a different viewpoint: time-course of the placebo effect. According to this study, the placebo effect for pain showed a unique pattern: it increased gradually over 12 weeks, and then decreased as time passed. The effect was most prominent at 12 weeks, with a standardized mean difference of 0.74 (95% CI: 0.54–0.94) and was present even at 52 weeks. This magnitude of 0.74 is much greater than 0.42 found by Madsen et al.⁶, although both studies examined the same conditions (i.e., pain). It is now more apparent that the placebo effect of acupuncture is clinically meaningful.

Contrary to the placebo effect studies, there is only one study regarding the nocebo effect of acupuncture. In this study by Koog et al.¹¹ the nocebo effect, as detected by the rate of patients with any adverse event, was 0.049 (95% CI: 0.012–0.086) in risk difference. When this value was converted into a number needed to harm to seek the clinical relevance, 20 patients needed to be treated with placebo acupuncture to observe one additional adverse event and indicate the clinical relevance of the nocebo effect.

Considering all these data regarding the placebo and nocebo effects of acupuncture,^{6–11} it can be concluded that the two effects are significantly large in clinical situations. However, this conclusion is surprising, as the placebo and nocebo effects are conflicting notions. How can those opposing effects occur simultaneously in one intervention?

Interestingly, this situation also is observed in a trial by Kaptchuk et al.¹³ that examined effect of placebo acupuncture versus placebo pill. It showed that the placebo acupuncture had larger effects on pain outcomes as compared with the placebo pill. It also reported that 15% and 20% of participants, respectively, complained of adverse events for the placebo acupuncture and placebo pill. The same issue with this trial has been reported by Sedgwick, who noted that the two effects occurred simultaneously with the placebos in one trial.¹⁴

Accordingly, the placebo and nocebo effects may not be separate in acupuncture.¹⁵ If so, then the effect of placebo acupuncture over no-treatment may not be the pure placebo or nocebo effects. Furthermore, if these two effects should be considered for evaluating the efficacy of acupuncture, findings of clinical trials may also be biased. Therefore, it is necessary to consider the effect of placebo acupuncture over no-treatment in relation to these two effects. Below, this effect will be examined by means of a simple mathematical model.

2. simple additive model

In its simplest form, the model is based on a condition for which two treatments – placebo acupuncture and no-treatment – were provided. It is assumed that, with regard to the purely physiological effect, placebo acupuncture and no-treatment benefit, on average, a proportion (O) of eligible people. If the placebo effect for acupuncture does exist, it would bestow an extra average advantage for placebo acupuncture of an amount (P), yielding O + P. Conversely, if the nocebo effect for acupuncture does exist, then it would bestow an extra average disadvantage for placebo acupuncture

Table 1
Effect of placebo acupuncture and no-treatment.

	People indifferent	People for placebo effect	People for nocebo effect
No-treatment	O	O	O
Placebo acupuncture	O	O + P	O – N

Effect of placebo acupuncture over no-Treatment: $\alpha P - \beta N$
($\alpha + \beta + \gamma = 1$, where α is the proportion of eligible population responding to placebo effect, β the proportion responding to the nocebo effect, and γ the proportion characterized as indifferent.

ture of an amount (N), yielding O – N. These effects are summarized in Table 1.

If the proportion of the eligible population that responds to the placebo effect is α , and the proportion β responds to the nocebo effect and the proportion γ is characterized as indifferent, then it follows that $(\alpha + \beta + \gamma) = 1$. By subtracting the estimated mean effect in placebo acupuncture group from that in no-treatment group, the effect estimate of placebo acupuncture over no-treatment then will be:

$\alpha P - \beta N$

If αP is greater than βN , then this estimate would be positive. Conversely, if αP is less than βN , then the estimate would be negative.

This model is different from the conventional concept, in which the placebo and nocebo effects are calculated separately. To date, these effects have been determined by using either positive or negative outcomes. However, the current model incorporates both of the effects in a single expression without paying attention to the nature of outcomes.

It may be wondered how opposing effects can occur in a single outcome. However, there is evidence that placebos were positively effective in regard to pain outcomes along with positive suggestions¹⁶ and were negatively effective on the same outcomes in the presence of negative hints.¹⁷ These conflicting results suggest that, depending on circumstances, participants receiving placebos can respond in opposite directions. From the current model, the opposite responses can be explained by the proportions of population who respond to the placebo and nocebo effects (i.e., α and β).

3. Example

For the sake of convenience, let us assume the magnitude of P and N to be same. This assumption is reasonable when considering that the magnitudes of the placebo and nocebo effects for pain are similar. For example, the placebo effect induced by verbal suggestions was 0.85 in magnitude,¹⁶ whereas the corresponding magnitude of the nocebo effect was 0.90.¹⁷ The placebo and nocebo effects induced by a combination of verbal suggestions and conditioning were also 1.45¹⁶ and 1.22¹⁷ in magnitude, respectively. Specifically, Petersen et al.¹⁷ pointed out that the comparable magnitudes for the two effects may be due to similar mechanisms involved in the opposite effects. In fact, there is evidence that the placebo and nocebo effects are opposite responses of dopaminergic systems and endogenous opioid neurotransmission in a distributed neural network.¹⁸

However, in general efficacy trials, participants are typically informed of the study aim, and thus expect to gain health benefits from treatments. Therefore, it can be expected that α is greater than β in the efficacy trials. If the two effects are 0.9 in magnitude and if 20% respond to the placebo effect and 10% to the nocebo effect, the effect of placebo acupuncture over no-treatment will be

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