Letter to the Editor

Reply to “The discussion on the validity of sham controls and patient blinding in a sham-controlled acupuncture trial” [Integr Med Res 2022; 11: 100795]

In a letter to the editor by Ge,¹ the author raised the issues in our study² concerning the patient blinding and sham intervention, which critically affect the methodological quality of sham-controlled randomized clinical trials.

The first issue raised was about patient blinding. The author raised objections to the time point of the blinding tests. In the original article,² we described that the blinding test was administered after the first intervention. It was pointed out that this time point was unusual and the measurements would be more reasonable if they occurred at the end of the study. However, in fact, we conducted blinding tests not only after the first intervention but also after the final intervention at week 8, as described in our protocol paper.³ The blinding index shown in Table 4 of the original article² was obtained from the blinding survey conducted at week 8. We regret that the time points of the blinding tests were incompletely described in the article. The blinding index presented in Table 4 of the original article was calculated from the blinding survey that was conducted after the final intervention, not after the first intervention. The table is updated with the results of the blinding survey conducted after the first intervention and after completing the final intervention (Table 1).

In the treatment group (TG), 14 patients participated in the blinding test after the first intervention and 13 patients participated in the blinding test after the final intervention. After the first intervention, 11 patients (78.6%) believed that they had received the real treatment, 1 patient (7.1%) misconjectured that the person had received the sham intervention, and 2 patients (14.3%) answered that they had no idea. After the final intervention, 8 people (72.7%) believed that they had received the real treatment, 1 person believed that the person had received the sham intervention (9.1%), and 2 people (18.2%) answered that they did not know which intervention they had received. In the case of the control group (CG), 16 people participated in the blinding test after the first intervention and 13 participated in the blinding test after the final intervention. After the first intervention, 9 people (56.3%) misconjectured that the intervention they had received was the real treatment. Only 3 people (18.8%) correctly projected that they had received the sham intervention, and 4 (25.0%) answered that they had no idea. After the final intervention, 11 patients (84.6%) misconjectured that the intervention they received was the real treatment, only one patient (7.7%) correctly predicted that they had received the sham intervention, and 1 patient (7.7%) answered that they did not know which intervention they had received.

Taken together, the majority of the participants in both the TG and CG believed that the intervention they had received was real treatment. In particular, in the case of the CG, more participants misconjectured that they had received the real intervention at week 8 than at week 1, indicating that patient blinding was successfully achieved in the CG. Considering that wishful thinking as observed in this study is considered one of the ideal blinding scenarios that can minimize bias in randomized controlled trials (RCTs),⁴ we think the concerns about the possible failure of patient blinding in the CG of this study can be addressed.

The second issue raised was about the feasibility of the sham device. The author pointed out the possibility that it would be difficult to blind the patients for 8 weeks when they received a real or sham intervention in a visible location, which we think is a reasonable suspicion. However, first, the patients did not know where the effective treatment points were actually located. Second, we tried to prevent the patients from recognizing whether the intervention was real or sham by the appearance of the devices. Therefore, we used seemingly identical moxibustion devices in both groups as shown in Figure 3 of the protocol paper.³ For the sham acupuncture intervention, Park sham placebo device was used, which ensured patient blinding by making it difficult for the patients to notice whether the tip of the acupuncture needle had pierced the skin or not. As described above, fortunately, the negative predictive rate was very high in the CG, indicating that patient blinding was successful in the sham CG.

The real concern, rather than patient blinding, as the author also pointed out, is that the sham intervention may not have been a real “sham”. Although several sham acupuncture devices have been developed, including the one we used, they are not completely inert, and even tend to intensify the nonspecific effects of acupuncture, sometimes leading to the failure of acupuncture clinical trials.⁵ The main opinion of experts in this field is that there is no ideal sham acupuncture device that does not cause any physiological activity.⁵ It is also known that quality-guaranteed sham moxibustion devices have not yet been developed,⁷ so we developed our own sham moxibustion device.³ Despite our efforts to block heat transfer from the sham device, it seems that there was a substantial thermal stimulus in the sham moxibustion device, as we have described in the article.³ We strongly agree that the development of appropriate sham devices for acupuncture and moxibustion is urgent.

While discussing the second issue, the author also pointed out that there were significant differences in the Hamilton Rating Scale for Depression (HRSD) values between the TG and CG at baseline, noting that this could also affect the results of this study. This is a fact that we also acknowledge as one of the limitations of this study, so the second paragraph of the Discussion section of the original article² described this issue. As we have already mentioned there, this issue is a possible problem of RCTs with small sample sizes and is the reason why we decided to use analysis
of variance (ANCOVA) with a baseline value set as covariates beginning in the design phase of this study. By using this statistical technique, the results of the comparison of posttreatment values between the two groups were corrected for differences in the baseline. Therefore, despite the baseline differences, the results of this study are statistically reliable.

In summary, we agree with the comments raised by Ge, and in order to clarify about the blinding of our study, the detailed description is added in Supplement.

Supplementary materials

The detailed description about the blinding of the study which are added in “2.4 Blinding” section and “3.7 Blinding index” section can be found in the online version, at doi:10.1016/j.imr.2022.100837.

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