Randomized Trial

Randomized Placebo-Controlled Placebo Trial to Determine the Placebo Effect Size

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Background: It is the gold standard to use a placebo treatment as the control group in prospective randomized controlled trials (RCTs). Although placebo-controlled trials can reveal an effect of an active treatment, the pure effect of a placebo treatment alone has never been presented or evaluated. No evidence-based, placebo-therapeutic options are currently available, and no placebo-controlled trials have been performed to elucidate the pure placebo effect.

Objectives: To analyze the pure placebo effect on clinical, chronic pain through a blinded RCT.

Study Design: A prospective, randomized, placebo-controlled trial.

Setting: Medical University centers.

Methods: One-hundred eighty-two patients suffering from chronic plantar heel pain for over 6 months,who failed to respond to conservative treatments, were screened and 106 of these patients were enrolled into this study. The patients were randomly assigned to receive either a blinded placebo shockwave treatment or an unblinded placebo shockwave treatment. The primary outcome measure was the differences in percentage change of visual analogue scale (VAS) scores 6 weeks after the intervention. The secondary outcome measure was the differences in Roles and Maudsley pain score (RMS) 6 weeks after intervention. As an exploratory outcome, 2-sided group comparisons for baseline characteristics between active treatment and controls were done using the Mann-Whitney-U tests for group comparisons; treatment efficiency was calculated by the effect size coefficient and benchmarks for the Mann-Whitney estimator according to the t-test of 2 independent samples for quantitative data, as well as the Fisher's exact test for binary data.

Results: Patients from both groups did not differ with respect to heel pain ratings at baseline, for both the VAS (P = .476) and RMS (P = .810) scores. After 6 weeks, patients receiving the blinded placebo treatment reported less heel pain on both scales (VAS: P = .031; RMS: P = .004). Change scores of pain ratings were significantly higher in the blinded placebo group than in the un-blinded placebo group (VAS: P = .002; RMS: P = .002).

Limitations: As the study represents the first to use an inverse placebo RCT (IPRCT), further conceptual and methodological issues need to be addressed to describe detailed, underlying mechanisms. Specific contextual, intrapersonal, and interpersonal factors modulating the placebo effects should be addressed in future IPRCTs.

Conclusion: The present study indicated that true placebo effect sizes can be analyzed through a proper IPRCT design. Instead of treating high numbers of patients with placebos in a RCT, which increases the risk for subjects not receiving the active treatment, the IPRCT technique seems to be much more appropriate to analyze the effect sizes of any active treatment, in accordance with the Good Clinical Practice guidelines and Declarations of Helsinki.

Key words: Pain, randomized controlled trial, RCT, placebo, effect size, inverse placebo, study, pain therapy

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For many years, placebos have been conceptualized by their inert content and their use as controls in clinical trials and treatments in clinical practice (1). The word "placebo" comes from the Latin verb "placere" (pleasing), and is used in medical context meaning innocuous treatment to make a patient comfortable." Placebos have been used as a non-specific but effective application in therapeutic treatments (2-5). Due to the powerful effects of the treatment itself (6), the gold standard in randomized controlled trials (RCTs) is to include a placebo-control condition (7,8). A placebo-controlled trial can show both the existence of an effect and illustrate the absolute effect sizes (9).

In pain treatment, it is well documented that a placebo treatment can induce the so-called placebo analgesia (PA). PA induces discrete physiological changes mediated by the endogenous opioids system (10-14). Functional imaging reveals that the belief of being treated with analgesia leads to a reduced anticipatory activation of the central pain network in response to an experimentally-induced painful stimuli. This reduced anticipatory activation is often accompanied by the reduced sensation of acute pain (15-17). Here, the PA is used in many ways, e.g., in diabetic neuropathic pain (18), dental pain (19), migraine (20), fibromyalgia (21), or pancreatic pain (22).

Plantar fasciitis is the most common cause of heel pain. Non-surgical treatment is successful in about 90% of patients. Many of the remaining patients will require surgery, with long recovery times, and are exposed to an additional risk of complications (23,24). The most promising non-surgical treatment, with the highest quality of evidence supporting its use, is extracorporeal shockwave therapy (ESWT) (25-27). In an earlier placebo-controlled RCT, our group reported that ESWT reduces plantar heel pain remarkably (25,28,29). In this present study, we are interested in investigating whether a sham ESWT might, by itself, be able to induce PA in patients with plantar heel pain.

In placebo-controlled RCTs, to prove the effectiveness of an active treatment (verum effect), it is recommended to design the verum and placebo conditions to be as comparable as possible, with the same setting, same provider, homogenous groups, cross-over trials, double-blinded conditions, and so forth (30). Such efforts often lack at comparability in controlling for the actual placebo effect. For example, in 3-arm clinical trials the verum and placebo conditions are compared with a no-treatment condition (31-33). In these no-treatment conditions patients know that they do not receive an effective treatment, and consequently no placebo effect can be expected (34-36). Although these studies are designed to prove the actual placebo effect, a no-treatment condition often includes confounding factors which can affect the outcome measurement of the no-treatment groups seriously (e.g., "attrition bias," "response bias," "compensatory rivalry," "resentful demoralization," or nocebo effect) (30,37-39). To the best of our best knowledge, no placebo-controlled study thus far has proven the placebo effect itself by using the same placebo intervention in both arms of a study, differentiating between the 2 arms solely by having the patients in one arm believe, in a tightly controlled setting, that they are being treated. The aim of the present study was to investigate the actual placebo effect in pain treatment. To analyze the effect of the placebo treatment itself, we created a new study design which we have called an "inverse placebo randomized controlled trial" (IPRCT) design. The goal of an IPRCT is to prove the effect of placebo treatment itself by comparing 2 placebo conditions in identical therapeutic settings. Patients suffering from plantar heel pain were divided into 2 groups. Both groups were treated with placebo ESWT, but the first group was told that they would receive a placebo ESWT treatment (placebo treatment – placebo information); the second group was told that they would receive a verum ESWT treatment (placebo treatment – verum information). We hypothesized that only the patients of the placebo-verum condition would display placebo-induced hypoalgesia.

Methods

The study was conducted after submission to the Intendant Ethic Review Board and was designed in accordance with the guidelines of Good Clinical Practice. The study was also designed in accordance to guideline E6 of Good Clinical Practice of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). All patients gave written informed consent. The hypothesis was that there is no difference in effectiveness between verum-placebo and placebo-placebo treatment in patients suffering from chronic heel pain. The study was registered in the German Clinical Trial register (DRKS00011643).

Participants

The participants were outpatients of a university Department of Orthopedic Surgery and Sportstraumatology. All of the patients reported a history of chronic plantar heel pain. Patients were included if they report-

ed a history of at least 6 months of unsuccessful conservative treatment. Non-pharmacological treatments included physical therapy (e.g., ice, heat, ultrasound, iontophoresis, or electromyostimulation), physiotherapy (e.g., massage and stretching), over-the-counter devices (e.g., orthosis, tape, or heel pads), shoe modification (e.g., higher heels), immobilization (e.g., cast), and night splints. In the case of pharmacological treatments, the following methods were tolerated: external application of analgesics and/or anti-inflammatory gels, therapy with prescription analgesics and/or non-steroidal anti-inflammatory drugs (NSAIDs), and local injections of anesthetics or corticosteroids. Corticosteroid injections were ceased for at least 6 weeks before the onset of the study, anesthetic injections, iontophoresis, ultrasound and electromyostimulation were ceased for at least 4 weeks, NSAIDs for at least one week, and prescription or non-prescription analgesics, heat, ice, massage, stretching, and night splinting for at least 2 days. Further exclusion criteria were nerval disturbance, diabetes mellitus, complex regional pain syndrome, anticoagulant therapy, incomplete conservative therapy, persistent infection, skin lesion, tumor, disturbance of coagulation, lung tissue in direction of shockwave, or pregnancy.

While 182 patients were assessed for eligibility within an 18 month period, a total of 106 patients fulfilled the study criteria and participated in this prospective randomized placebo-controlled study (Fig. 1). All patients (64 women), aged 31-75 years (M = 50.1; SD = 9.9), were assigned either to a placebo-verum (n=53; 32 women) or a placebo-placebo (n = 53; 32 women)

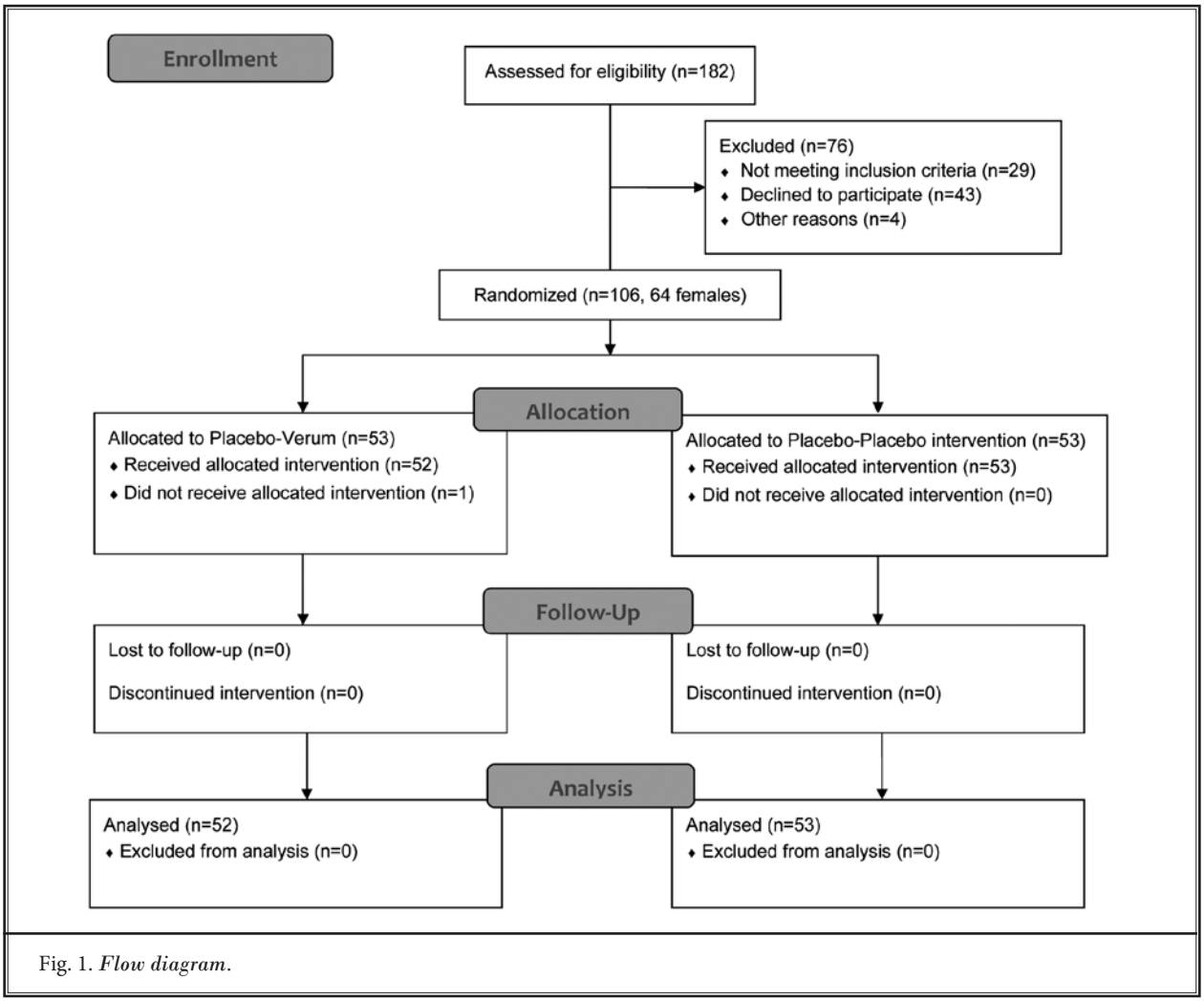


Fig. 1. *Flow diagram.*

Table 1. *Participants´ characteristics*.

Groups	Placebo-Verum	Placebo-Placebo	Placebo-Verum vs. Placebo-Placebo	Effect size	Confidence Interval of Effect Size
	M (SD)	M (SD)	*P*		95% CI
Age	51.0 (10.5)	49.3 (9.4)	.519[a]	.537[b]	.427 to .646 [b]
Duration of pain (months)	18.4 (19.3)	18.2 (21.6)	.944[a]	.505[b]	.396 to .613 [b]
BMI	27.9 (5.2)	28.5 (5.6)	.729 [a]	.545[b]	
	n	*n*			
Location (left:right)	17:35	19:34	.733[c]	-.032[d]	-.213 to .150 [d]
Gender (females:males)	32:20	32:21	.903[c]	.012[d]	-.175 to .198 [d]

Note: ESWT, Extracorporeal shockwave therapy; M, mean; SD, standard deviation; a, results of 2-tailed Mann-Whitney-U test; b, effect sizes in terms of Mann-Whitney estimator with 95% CI; c, results of a Pearson´s Chi-Quadrat test; d, rate difference with 95% CI.

with concealed allocation in permuted blocks of 4 – 8 with the use of a computer-generated random list. Concealment of randomization was guaranteed by non-transparent envelopes. Whereas the treating physician was un-blinded, both the patients and the evaluating physicians were blinded to randomization. The groups did not differ with respect to age, duration of pain, afflicted site, body mass index (BMI), or gender distribution (Table1).

All of the patients were told that they were participating in a placebo-controlled study to determine the effect of ESWT on heel pain sensations. They were all informed about the benefit of ESWT on heel pain using a standardized briefing letter. Next, patients were asked to rate their acute heel pain using a visual analog scale (VAS; ranging from zero: no pain at all to 10: unbearable pain) as well as the Roles & Maudsley Scale (RMS; 4-point ordinal scale: 1, very good; 2, good; 3, fair; 4, poor). Immediately after the pain ratings, patients were randomly assigned to either the placebo-verum or to the placebo-placebo group. The patients of the placebo-placebo group were informed that the subsequent placebo treatment would have no effect, while the patients of the placebo-verum group were told that they would be treated by real and effective ESWT. Both groups, however, underwent the same sham ESWT. The usual clinical stimulation protocol was performed; 2000 shockwaves were delivered at a frequency of 8 Hz and applied at the maximum tender points. However, the applicator was modified in order to reduce the application pressure from 4.0 bars to 0 bars, while still providing tactile sensations, such as vibrations, to the patients. This ESWT placebo technique has been proven by a number of placebo-controlled randomized trials (29,40-45). Directly after shockwave treatment, all of the patients were asked which treatment they believed they received, to analyze the placebo-blinding efficacy. The primary criteria were defined as a change in pain sensation due to heel pain using a VAS as well as a RMS. After reaching the primary study end-point of 6 weeks after treatment, patients who still suffered from significant heel pain were offered to be de-blinded for further interventions.

Statistical Analyses

The sample size calculation was based on the model of stochastic superiority within the Wilcoxon-Mann-Whitney test for the primary outcome measure "percentage change of VAS score." The following stipulations were made: relevant effect size MW = 0.64, alpha (one-sided) = 0.025, and beta (power) = 0.10. Due to usual ambiguities of the study (dropout, etc.) the sample size for the study was enhanced to N = 52 per group.

To measure the impact of PA, we compared baseline ratings, ratings 6 weeks after treatment, and change scores (i.e. the difference between baseline and delayed ratings after 6 weeks). Mann-Whitney-U tests were used for group comparisons; treatment efficiency was calculated by the effect size coefficient r=U/(n1*n2) (46,47), Mann-Whitney estimator according to Colditz and colleagues (48). The effect sizes were defined as: no difference < 0.56, small effect < 0.64, medium effect < 0.71, and large effect > 0.71 (42). The Mann-Whitney-U test was also used to compare age, the duration of pain, and BMI between groups. Distributions of gender and location (left/right) were analyzed by chi-squared tests in which effect sizes were calculated as $\phi = \sqrt{X^2/n}$.

In order to keep the multiple level of alpha, efficacy of the verum-placebo treatment was confirmed if both primary criteria of effectiveness (VAS score as

well as RM score) show a statistically significant result. A value of $P < 0.025$ (one-sided) was considered statistically significant.

Results

Patients of both groups did not differ with respect to heel pain ratings at baseline on VAS [U(103)=1268.5, Z=-.71, P = .476] or on RMS [U(103)=1352, Z =-.24, P =.810] (Table 2). After 6 weeks, however, the patients from the placebo-verum group (patients who received placebo and were told that they were receiving ESWT) compared to the patients of the placebo-placebo group (patients who received placebo and were told that they were receiving placebo) reported less heel pain, both on VAS [U(103)=1044, Z=2.16, P = .031] and on RMS [U(103)=982.5, Z=-2.89, P = .004]. Moreover, the change in ratings from baseline to 6 weeks after treatment was higher in the placebo-verum group than in the placebo-placebo group [VAS: U(103)=915.5, Z=-3.13, P = .002; RMS: U(103)=979, Z=-3.14, P = .002] (Fig. 2).

With regards to the blinding technique after shockwave treatment, all patients were asked which treatment they thought they received. In the placebo-verum group, 48 out of 53 patients (90.6%) thought they received the promised verum intervention, while in the placebo-placebo group 49 out of 53 patients (92.3%) believed they took part in the placebo intervention. The 2 groups did not differ with respect to their belief in being assigned to the promised study arm [$\chi 2(1)$ = 0.1, P = .7].

Discussion

By introducing a new placebo-controlled study design, this study showed that the belief of being treated by an effective treatment solely modulates placebo-induced hypoalgesia in heel pain. While both patient groups were treated by the same placebo ESWT, only the patients who were told that they would be receiving the active treatment (placebo-verum) displayed placebo-induced hypoalgesia, whereas the patients being correctly informed about the placebo treatment (placebo-placebo) did not report a placebo-induced analgesia.

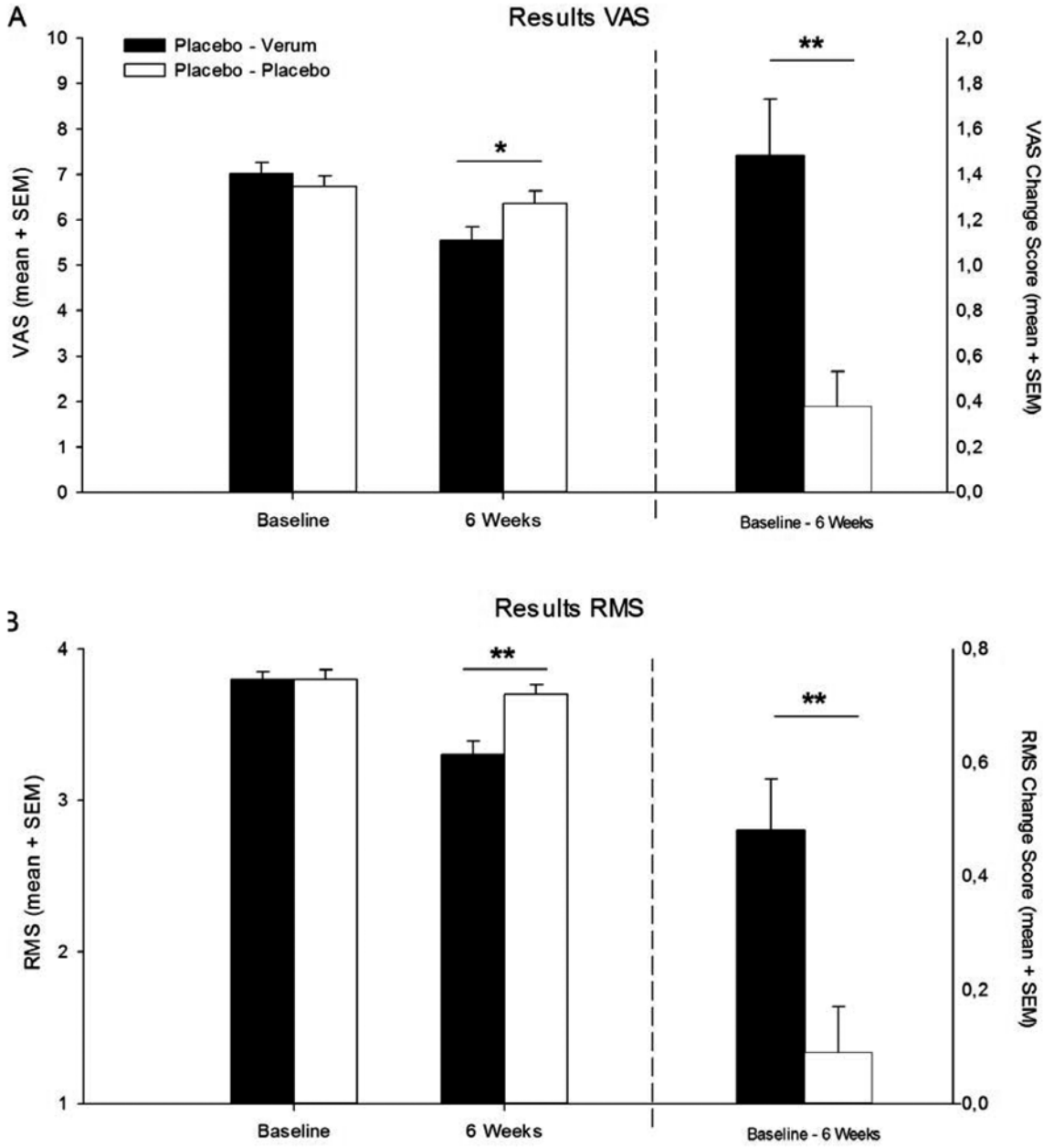
The pain rating data of the placebo-verum group were in line with several other randomized controlled trials (RCT) reporting a reduced pain sensation after placebo treatments (25,28,40,49). Interestingly, only one single treatment was sufficient at inducing a reduced pain rating 6 weeks after intervention in this study. As hypothesized, patients from the placebo-placebo condition did not show relevant symptom improvements over 6 weeks. Also, this finding is consistent with other studies in that the placebo effect is only observable when patients (or their physicians) believe that the proper treatments are being performed (34-36,50,51). Therefore, placebo ESWT may be considered here as a promising, additional therapeutic option in the treatment of heel pain.

It is known that placebo responses in RCTs can be confounded by spontaneous symptom improvements. A meta-analysis of 3-arm trials, including a "no treatment" control group, in 8 different clinical conditions revealed that about 50% of the placebo responses could be explained by spontaneous remissions or variations (52). If spontaneous symptom improvements affected the results of the present study significantly, then this should have been true for both groups in a similar way. Since both groups did not differ with respect to well-

Table 2. *Results of subjective pain ratings.*

Subjective Pain Rating	Placebo-Verum	Placebo-Placebo	Placebo-Verum vs. Placebo-Placebo	Effect size	Confidence Interval of Effect Size
	M (SEM)	M (SEM)	P	MW	95% CI
VAS					
Baseline	7.0 (.24)	6.7 (.24)	.476	.460	.352 to .569
After 6 weeks	5.5 (.31)	6.3 (.28)	.031	.621	.513 to .729
Change score	1.5 (.25)	.38 (.15)	.002	.668	.566 to .770
RMS					
Baseline	3.8 (.05)	3.8 (.06)	.810	.491	.414 to .567
After 6 weeks	3.3 (.09)	3.7 (.06)	.004	.644	.549 to .738
Change score	0.5 (.09)	0.1 (.08)	.002	.645	.559 to .731

Note: ESWT, Extracorporeal shockwave therapy; M, mean; SEM, standard error of means; VAS, Visual analogue scale; RMS, Roles & Maudsley Score; *P*-values refer to results of 2-tailed Mann-Whitney-U test; effect sizes in terms of Mann-Whitney estimator (MW) with 95% CI.



Note: A, results of ratings on VAS, visual analogue scale; B, results of ratings on RMS, Roles & Maudsley Score; ESWT, Extracorporeal shock wave therapy, SEM, standard error of means; *, $P < .05$;**, $P < .01$.

Fig. 2. *Results of subjective pain ratings.*

known potential mediators of placebo responses as to age, gender, or disease severity at baseline (4,53-55), a random allocation of highly suggestible patients to the placebo-verum condition seems very unlikely. Moreover, it seems unlikely that uncontrolled symptom improvements affected the results of the present study, since we did not see any substantial changes in pain ratings in the placebo-placebo group. Similarly, a patient's assessment of the applied therapy after 6 weeks revealed that in both groups more than 90% (90.6% vs. 92.3%) of all patients were convinced to be taking part in the study arm they were assigned to. This demonstrated not only

the high efficiency of the blinding technique but also the excellent homogeneity of blinding rates between both groups. Systematic reviews of clinical trials comparing placebo with no treatment groups revealed that there was a positive effect for placebo in trials with subjective assessment criteria (especially in the treatment of chronic pain), but this effect diminished in larger sample sizes (n > 100) (56,57). Since the sample size in the present study was large (n = 105), the findings of the present study should be considered robust.

Our results provide insight in the powerful nature of human belief in being treated and open a new field of study designs. Placebo studies can improve their conclusions by making the placebo and its control condition as similar as possible by solely varying the information about the treatment. In a similar fashion, active treatment studies can also benefit from this actual placebo effect. By knowing the impact of placebo, clinical trials should change the design in favor of the patient's risks not to receive an inactive medication. Instead of controlling a verum effect by introducing similar designed (but sometimes risky) placebo condition, researchers could alternatively design 2 verum conditions as follows: while in the one verum condition, patients would be told that they are receiving an active treatment (verum-verum) and in the second condition patients would be told that they are receiving a placebo, although both of the conditions would receive the same active treatment (verum-placebo). Such a new IPRCT implicitly navigates around several ethical issues which are associated with classical placebo-controlled RCTs. According to the Declarations of Helsinki, the use of placebo-controlled conditions in active treatment or clinical trials are only allowed under certain circumstances (e.g., when no other proven intervention exists and when there is no risk of serious or irreversible harm by withholding the best intervention) (58). Thus, the use of an IPRCT is in line with the Declarations of Helsinki, since all patients can receive the same intervention without withholding the best active treatment. In the same way, study designs based on the IPRCT are in accordance to the International Conference on Harmonisation (ICH) guidelines. Modern studies can calculate the real treatment related effect sizes (verum-verum) by determining the (real) placebo effect size (verum-placebo) and subtracting the real placebo effect size from the overall effect size. In addition to a proper control of placebo effect by a suitable study design, every placebo study should also include an assessment asking whether or not patients are convinced that they are taking part of the study arm they were assigned to at the beginning of the study. With regards to the blinding technique after shockwave treatment, all patients were asked which treatment they thought they received. In our placebo-controlled placebo trial we have tested the blinding efficacy. There was no statistical significant difference found between both groups with regard to the awareness about the received treatment (P = 0.7). No clinical placebo-controlled trial can show any efficacy for any treatment until it is proven that the enrolled patients truly believe that the treatment is congruent with the assigned study arm. The next step should be to re-evaluate our findings within a modified 4-group study design: group 1: active treatment – the patients are told that they will receive active treatment, group 2: active group – the patients are told that they will receive placebo treatment, group 3: placebo treatment – the patients are told that they will receive placebo treatment, group 4 placebo treatment – the patients are told that they will receive active treatment. Through this, it´s assumed that active effect sizes and the real placebo effect size can be determined with higher reliability. In addition, the IPRCT approach is suitable to prove effect sizes in the same way but with significant reduction on the number of patients treated with placebos.

Since this study is the first to use an IPRCT, further conceptual and methodological issues need to be addressed to describe the underlying mechanisms in more detail. Several contextual, intrapersonal, and interpersonal factors modulate the placebo effect (see "enhanced placebo effect," "device-related placebo effect," "provider-related placebo effect," patients´ characteristics, etc.) (4,59-62). Therefore, systematic studies are required to not only replicate our findings, but to also elucidate under which circumstances the IPRCT acts most with the largest impact. Standardized and detailed treatment manuals (including characteristics of the target group, rules for communication/interaction, time schedules, selection of materials, devices, etc.) (4,18,59,60,63-65) are necessary to ensure maximal transparency and comparability.

Taken together, the present study shows that the real placebo effect size can be analyzed by using a proper IPRCT design. Precise knowledge of the placebo effect size is mandatory to make any statement regarding any active treatment modality in a clinical trial by determining the efficacy of blinding techniques in clinical RCTs. It is also mandatory to analyze the patient's awareness of the received treatment to test the blinding efficacy. Instead of treating high numbers of

patients with placebo in placebo-controlled RCTs and increasing the risk of not receiving an active treatment in RCT, the IPRCT technique offers the ability to analyze both the presence and the size of any treatment effects, in a manner which is in accordance with the Good Clinical Practice guidelines as well as the Declaration of Helsinki.

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