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BRIEF REPORT

Open-label Placebos for Wound Healing: A Randomized Controlled Trial

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Abstract

Background Open-label placebos are a novel treatment option, in which participants take placebos with full knowledge that they do not contain active medicine. Open-label placebo treatments have been shown to result in patient-reported symptom improvements, but they have not been tested on objectively measurable physiological outcomes such as wound healing.

Purpose The current study aimed to determine whether open-label placebos improved wound healing in punch biopsy wounds compared with no treatment.

Methods In a randomized controlled trial, 70 participants (mean age 27.6 ± 10.1, 58 female) were provided with information about the beneficial effects of placebos and given a 4 mm punch biopsy wound. Participants were then randomized to either an open-label placebo intervention (two placebo tablets twice a day for 10 days) or a no-treatment control group. Wounds were photographed at 7 days and 10 days to determine reepithelialization of the wound surface.

Results No significant differences were observed between the open-label placebo and control conditions in the percentage of wound area healed or for the number of participants with fully reepithelialized wounds at 7 days (placebo 7/32 wounds healed, control 10/33 wounds healed, (χ^2[1, N = 65] = 0.60, p = .440, φ = 0.10) and 10 days after wounding (placebo 17/32, control 25/33 wounds healed (χ^2[1, N = 65] = 3.64, p = .056, φ = 0.24).

Conclusions Open-label placebo treatment does not improve the healing rate of wounds. Open-label placebos may be beneficial for subjective patient-reported outcomes but do not influence wound healing.

Australian New Zealand Clinical Trials Registration ACTRN12616000411448.

Keywords Open-label placebos • Placebo response • Wound healing • Reepithelialisation • Randomized controlled trial

Placebo treatments have been well established as beneficial for subjective symptoms such as pain [1]. Placebos can also improve physical functionality [2] and objectively measurable physiological outcomes for some inflammatory conditions including duodenal ulcers [3] and ulcerative colitis [4]. Placebo use is safe, with low risk of harm, and effective for various outcomes. However, it is considered unethical to deceptively provide placebos instead of an active treatment as this violates the principle of informed consent and may undermine the relationship between the patient and health professional [5]. Despite ethical concerns, numerous studies show that a large percentage of healthcare professionals have used placebos in their medical practice [6].

Ethical concerns are alleviated if placebos are prescribed to patients without deception. A randomized controlled trial of open-label placebos for irritable bowel syndrome found self-reported global improvement in illness symptoms for patients who were given

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open placebo tablets compared with no-treatment controls [7]. Patients were informed that they were taking placebo medication with the expectation that they would be beneficial, established by describing how the placebo effect works through a mindbody healing process. Self-reported improvements were also found in open-label placebo trials using a similar paradigm for chronic lower back pain [8] and allergic rhinitis [9]. A recent review of five studies found a positive medium-sized effect for open-label placebos. [10].

No trials so far have been conducted for open-label placebos for objectively measurable physiological outcomes. For open-labelled placebos to be used in clinical care, it is important to determine the extent to which they are effective beyond patient-reported outcomes. It is possible that placebos may be simultaneously perceived as beneficial from self-report measures while having negligible effects for objectively measurable outcomes [11].

Wound healing is an objectively measurable outcome that is amenable to psychological interventions such as relaxation [12], expressive writing [13,14], and social support [15]. These studies show that systemic changes from psychological interventions result in improved wound healing times, even without physiological interventions directly affecting the wound site. Placebos are also a psychological intervention, which may operate on similar mechanisms to improve wound healing rates without direct physiological intervention. The punch biopsy is a commonly used experimental procedure to create minimally invasive dermal wounds and to study the effects of psychological stress on healing [16]. Since punch biopsy removes tissue, it has clinical relevance for other wound types that involve tissue loss such as injury or surgery.

The current study aimed to determine whether the reepithelialization rate of punch biopsy wounds in healthy participants improved with open-label placebo treatment compared with no treatment. Based on previous open-label placebo studies, we hypothesized that more participants in the open-label placebo condition will have fully reepithelialized wounds at 7 and 10 days following wounding than in the control no-treatment condition.

Method

Study Design and Participants

A randomized controlled trial was conducted between April and September 2016 comparing open-label placebos with no-treatment controls. The trial was registered at the Australian New Zealand Clinical Trials Registry (ACTRN12616000411448). Ethics approval was obtained from the University of Auckland Human Participants Ethics Committee (Ref 017036). Participants were recruited through advertisements requesting participation in a study on "placebos and wound healing." Inclusion criteria required participants to be nonsmokers aged between 18 and 65, who could read and write in English. Participants were excluded if they reported having medical conditions that would affect wound healing (e.g. eczema, psoriasis, anemia, or diabetes) or regular use of medications or treatments affecting wound healing (e.g. anticoagulants, nonsteroidal anti-inflammatories, topical steroids). An *a priori* power analysis determined 68 participants were required to achieve a power of 80% with $\alpha = 0.05$, given a moderate effect size of $d = 0.7$. This effect size was chosen on the basis of two recent studies showing that the healing of punch biopsy wounds could be improved by psychological interventions with effect sizes of $d = 0.82$ and $d = 0.77$, respectively [17,14]. Furthermore, a review on the effects of open-labelled placebos versus no treatment showed a pooled effect size $d = 0.88$ [10].

Initially, 209 people stated interest in participation. Of these, 117 did not respond or declined to participate; 11 were interested but unavailable during the scheduled times; 10 were excluded due to smoking status, health conditions, or medications; and one withdrew during the initial session prior to receiving the punch biopsy. See Fig. 1 for a flow diagram of participant involvement. The study was completed by 70 participants (mean age 27.6 ± 10.1, 58 females). The majority identified their ethnicity as New Zealand European (57%). Five participants were excluded due to their hydrocolloid bandage coming off for more than 24 hours prior to the first follow-up session, potentially affecting the healing rate and resulting in eschar formation, which obscured the wound. Two participants were unable to attend the first follow-up at 7 days and were measured at 8 days (both in the control group). Two participants were unable to attend the second follow-up at 10 days: one placebo group participant met at 9 days, and the other control group participant met at 11 days. These cases were retained in the analyses. The final analyses included 65 participants, with 32 in the placebo group (mean age 28.8 ± 12.2, 26 females, 17 NZ European) and 33 in the control group (mean age 26.7 ± 8.4, 29 females, 19 NZ European).

Procedure

Initial session

The first session took approximately 25 minutes. Participants were greeted at the research centre using a standard script, which provided an overview of the study, before completing written informed consent and a baseline questionnaire. After completing the baseline questionnaire, participants met with the dermatologist who described the efficacy of the placebo effect from a

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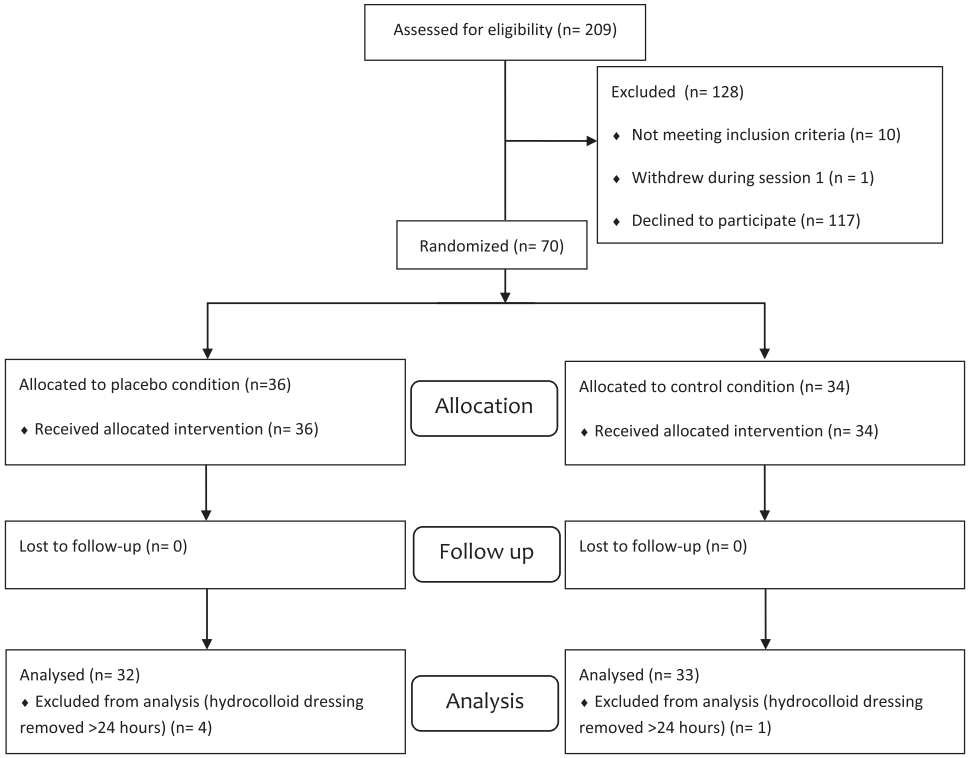

Fig. 1. Consort flow diagram of participant involvement.

script adapted from Kaptchuk et al. study [7], intended to establish an expectation that placebos would be beneficial. The dermatologist script was as follows:

> Studies have shown the placebo effect to be very powerful. This study is to determine whether the placebo effect can help heal wounds faster. A placebo is any type of treatment, like a pill, that doesn't contain any drugs or active ingredients. The placebo effect works because of two processes: conditioning and expectations. Over the course of our lives, we have all been to the doctor and been given pills, so our body learns to associate pills with healing, which is conditioning. The other way placebos work is through our expectations. Research shows that when we expect treatments to help, they are much more likely to be effective. Since your brain and immune system are highly connected, previous learning and expectations have a big influence on your immune functioning. For this experiment, we're testing how effective placebos are for wound healing.

The dermatologist then completed the wounding procedure, after providing an additional consent form specifically for the punch biopsy wound. The wound procedure involved creating a 4 mm punch biopsy wound on the inner upper arm, proximal to the medial epicondyle. The participants chose which arm to use: all but two participants chose the left arm. The wound was delivered under local anaesthetic (1% lignocaine with 1:200,000 adrenaline) and covered with a small hydrocolloid dressing (DuoDERM Extra Thin hydrocolloid dressing, ConvaTec) and an additional waterproof dressing (Opsite Post-Op, Smith & Nephew).

After the wounding procedure, the dermatologist opened an opaque envelope to allocate the participant to either the control group or the placebo group. The envelopes were numbered sequentially and prepared prior to study commencement by a researcher unrelated to the study based on a computer randomised list. Group allocation was carried out after the wounding procedure to ensure that participants were treated identically regardless of group allocation during the initial session, and the wounding procedure was not influenced by group allocation.

Participants in the no-treatment control condition were instructed not to take any additional treatments, just to wait for the wound to heal as normal. Participants in the placebo condition were provided with a 20 mL plastic vial labelled "Placebos" containing 40 tablets, with instructions to take two tablets twice a day starting the evening of the initial session. Participants were told that the tablets did not contain active ingredients. The tablets were provided by Douglas Pharmaceuticals: they were plain white, biconvex, 7 mm in diameter, and

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contained three standard ingredients for placebo pills (lactose monohydrate, microcrystalline cellulose and magnesium stearate).

Follow-up assessments

The first follow-up session was 7 days after the initial session and took approximately 10 minutes. In this session, the dressings were removed and the wound site cleaned. The wound was then photographed using a Canon DS126071 camera, with a Canon Ultrasonic EF 100 mm f/2.8 Macro USM lens and a separate Canon ring-flash attachment (Macro Ring Lite MR-14EX). Exposure was set to 1/125 s, ISO of 100, with an aperture of F20. After the photograph, the wound was covered with a hydrocolloid and waterproof dressing. The final follow-up session was 10 days after the initial session and took approximately 15 minutes. Participants first completed a follow-up questionnaire and were given a $20 shopping centre voucher. Then, the wound was cleaned and photographed, following the same procedure as the first follow-up session and dressings replaced with a regular adhesive bandage.

Measures

Wound healing

Wound healing was determined by the percentage of the wound healed and a dichotomous measure of healed or unhealed wound at 7 and 10 days, where full reepithelialization of the wound surface signified a healed wound. This was determined by a dermatologist, based on photographs of the wounds taken at 7 and 10 days. The photographs were presented without any participant or group information and identified only with random code numbers. A total of 130 photographs were analyzed, including one photograph from each of the two follow-up sessions for each of 65 participants included in the analysis. The dermatologist rated both the percentage area of the wound surface reepithelialized using National Institutes of Health ImageJ analysis software (version 1.51f) by outlining the total wound area, outlining areas that were not yet reepithelialized, and calculating the percentage area healed. Of the 130 photographs, 6 were determined to be not clear enough to allow for an accurate percentage healed rating, but a healed or not healed categorisation was completed on all wound photographs.

Other data

Demographic data collected at baseline included age, sex, ethnicity, and body mass index. Stress was measured by the 10-item Perceived Stress Scale [18]. We also collected data on the following health behaviours: alcohol and caffeine consumption measured by drinks per week, sleep duration, as well as sleep quality and diet quality rated on a scale from 0 "very poor" to 4 "very good." The follow-up questionnaire gathered data on adherence for the placebo participants on the number of doses missed. We also asked participants in the placebo group at the follow-up assessment "How helpful do you think the placebos have been to help your wound heal faster?" rated on a four-point scale from "not at all helpful" (0) to "very helpful" (3). Participants in the control group at follow-up were asked: "How disappointed have you felt that you were not taking the placebo medication?" also rated on a four-point scale from "not at all disappointed" (0) to "very disappointed" (3).

Statistical Analysis

Baseline data were examined for differences between groups using independent *t*-tests. The average percentage area of the wounds healed was not normally distributed at both day 7 and day 10; therefore, Mann-Whitney U tests were conducted between groups. Chi-square analyses were conducted to compare the number of wounds healed in each group.

Results

There were no significant differences between groups in baseline variables (see Table 1). Adherence to the placebo medication was high; 9 participants took all 20 doses, 15 participants missed 1–2 doses, and 7 participants missed 3–4 doses. No participants missed more than four doses.

At 7 days, there was no significant difference in the average percentage area of the wound healed between the placebo (mean rank = 30.26) and the control (mean rank = 33.69) groups ($Z = -0.75$, $p = .453$, $r = .10$; Fig. 2). There was also no significant difference in the number of wounds healed between the placebo (7/32 wounds healed) and the control group (10/33 wounds healed), ($\chi^2[1, N = 65] = 0.60$, $p = .440$, $\varphi = 0.10$). Similarly at 10 days, there was no significant difference in the average area of the wounds healed between groups (mean rank placebo 27.93, mean rank control 33.61; $Z = -1.54$, $p = .123$, $r = .20$; Fig. 2). The number of wounds healed in the placebo group was 17/32, whereas 25/33 wounds in the control group were healed ($\chi^2[1, N = 65] = 3.64$, $p = .056$, $\varphi = 0.24$).

Data from the follow-up subjective ratings showed that belief that the placebo had been helpful in those getting the placebo treatment was low at follow-up ($M = 0.90$, $SD = 0.70$). Also, data from the control group about how disappointed they were not to get the placebo treatment was also low ($M = 0.38$, $SD = 0.55$, suggesting that this was not a factor influencing the results).

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Table 1 Demographic and self-reported questionnaire information at baseline and follow-up showing average responses for 65 participants included in final analysis

	Open placebo (n = 32)	Control (n = 33)	Significance
	M (SD)	M (SD)	p
Baseline			
Age	28.8 (12.2)	26.7 (8.4)	.413
BMI	23.9 (4.5)	22.3 (3.7)	.122
Alcohol consumption (drinks per week)	4.8 (4.9)	4.2 (3.4)	.588
Caffeine consumption (drinks per week)	6.4 (4.5)	5.3 (5.4)	.364
Exercise (days per week)	3.4 (1.9)	4.1 (2.1)	.185
Diet quality	2.69 (0.7)	2.6 (0.8)	.669
Sleep hours	7.20 (1.1)	7.4 (1.0)	.397
Sleep quality	2.06 (0.6)	1.9 (0.5)	.519
Perceived stress	13.9 (5.6)	13.1 (6.0)	.544
Follow–up			
Alcohol consumption (drinks per week)	1.7 (2.4)	1.1 (1.7)	.244
Caffeine consumption (drinks per week)	3.7 (3.5)	2.7 (2.9)	.191
Exercise (days per week)[a]	2.7 (1.8)	3.6 (2.2)	.070
Diet quality	2.8 (0.7)	2.5 (0.9)	.823
Sleep hours	7.1 (1.2)	7.3 (1.0)	.566
Sleep quality	1.8 (0.6)	2.0 (0.7)	.332
Perceived stress	12.5 (6.6)	13.0 (5.9)	.720

[a]While this difference approached significance between the groups, exercise reported at follow-up was not significantly associated with the percentage of wound area healed at 7 days (r = 0.04, p = .755) or at 10 days (r = −0.04, p = .759).

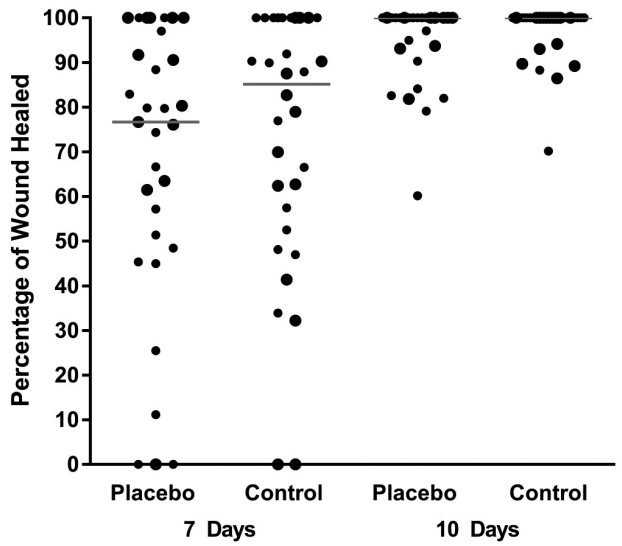

Fig. 2. Dot plot graph showing percentage of area healed for open-label placebo (n = 32) and control (n = 33) conditions at 7 and 10 day follow-up assessments.

Discussion

We found no significant differences between the placebo and control conditions for wound reepithelialization, indicating that open-label placebo treatment did not improve wound healing. There was no difference in wound healing between the placebo or control group at either follow-up point. The results cannot be explained by any measured baseline differences between the groups or low adherence to placebos.

The results of the current study contrast with previous research on open-label placebos. Previous trials have shown self-reported symptom improvements from open-label placebo treatment for irritable bowel syndrome [7], chronic lower back pain [8], and allergic rhinitis [9]. In contrast, the current study used an objectively measurable physiological outcome and found no benefit for open-label placebos. This suggests that open-label placebo treatments may not have the same beneficial effects for objective physiological outcomes than they do for patient-reported outcomes such as pain and symptom reports. This is consistent with previous reviews suggesting placebos are useful for modifying subjective states rather than curing disease or modifying pathophysiology [19]. The results are also consistent with a systematic review of 202 trials comparing placebo interventions with no treatment in 60 clinical conditions, which found that although placebos can influence patient-reported outcomes, such as pain

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and nausea, their effects did not substantially improve clinical conditions [20].

It seems likely that if open placebos did affect wound healing, the study would have been likely to detect this with the methodology we employed in the current study. A recent systematic review supports the ability of psychological interventions to influence wound healing, including experimentally created wounds in healthy participants, such as used in this study, as well as surgical, burn, and other wound types [21]. The current study also used a standard script to foster expectations about the healing power of placebos based on a previous study that had found open placebos to influence patient-reported outcomes [7].

Our study had a number of strengths. It was the first study to look at objective outcomes following treatment with open placebos. The design assigned group allocation after the wounding had taken place and maintained blinding for the researcher assessing wound healing. However, the limitations of the study should also be acknowledged. It should be noted that previous studies have used patient groups who may have been taking other treatments at the same time as the placebo medication. It may also be that patients getting treatment for a disease-related problem may be more motivated to improve their health problem and therefore more likely to respond to open placebos than an experimental sample [22].

A further limitation is that the study did not employ any biological markers of wound healing, such as matrix metallopropoteinase-9, collagen synthesis, or cytokine activity. It is possible that open placebos may have influenced biological activity, which would not have been picked up by our assessments. A further examination of healing after 10 days may have provided further information about the rate of healing in each group but is unlikely to have provided data inconsistent with the current findings. It should also be noted that we only relied on self-reported measures for diet, exercise, and sleep, and although these did not differ between groups, future research could include more objective validated instruments. The power analysis performed to calculate the required sample size was based on moderate effect size and a power of 0.80. If different assumptions had been made (either a smaller effect size or power of 0.90), this would have resulted in a larger required sample size, which would have given greater power to detect a smaller effect if one existed.

We found open-label placebos do not improve wound healing in a healthy cohort. While open-label placebos may be an effective treatment option for some subjective outcomes, they do not result in objectively measurable physiological changes. Further research would be required to establish whether they would be effective for other objective outcomes or a specific patient population. Their ethical use in clinical practice is only currently supported for patient-reported outcomes.

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Conflict of Interest Ashwin Mathur, Elizabeth Broadbent, Paul Jarrett and Keith Petrie declare that they have no conflicts of interests.

Compliance with Ethical Standards All procedures, including the informed consent process, were conducted in accordance with the ethical standards of the University of Auckland Human Participants Ethics Committee (Ref 017036) and with the Helsinki Declaration of 1975, as revised in 2000.

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