ANESTHESIOLOGY

Pain Response to Open Label Placebo in Induced Acute Pain in Healthy Adult Males

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Placebo treatments even if known to the patient to be placebo, so-called "open label placebo," may be effective in reducing chronic pain
- The effects of the extent of placebo education are poorly understood

What This Article Tells Us That Is New

- Using a well-characterized electrical pain sensitization model in human volunteers, the effects of short versus detailed placebo educational protocols were measured
- Open label placebo treatment reduced pain sensitization in the volunteers, but the extent of placebo education did not modify these responses

ABSTRACT

Background: Open label placebos with patient education are effective in reducing chronic pain, and recent studies on their effect on pain have established interest in this field. Nevertheless, data on their effect on acute pain are scarce, and on hyperalgesia and allodynia, absent. This study assessed the effect of open label placebos on acute pain in healthy adult males and the influence of placebo education.

Methods: Thirty-two healthy males were included in this prospective, randomized, assessor-blinded crossover, single-center study assessing pain intensities (*via* numeric rating scale), area of hyperalgesia (von Frey filament), and allodynia (dry cotton swab) in a pain model utilizing intracutaneous electrical stimulation. The authors compared the effect of intravenous open label placebo on pain compared to no treatment. The authors further examined the effect of placebo on hyperalgesia and allodynia, and the influence of education (short *vs.* detailed) before placebo application. Saliva cortisol concentrations were also measured.

Results: Pain ratings (median, first to third quartile) were 21% lower during placebo treatment compared to no treatment, 4.0 (3.2 to 4.9) *versus* 5.1 (4.7 to 5.4), respectively ($P = 0.001$). The areas of hyperalgesia and allodynia were lower during placebo treatment compared to no treatment (hyperalgesia, 30 cm^2 [17 to 47] *vs.* 55 cm^2 [42 to 68], $P = 0.003$; allodynia, 24 cm^2 [11 to 39] *vs.* 45 cm^2 [31 to 62], $P = 0.007$). This corresponds to reductions of 47%. The extent of placebo education had no effect on pain. Saliva cortisol decreased significantly over time and was under the limit of detectability in the majority of participants in postbaseline measurements in both treatment branches. Baseline cortisol was not associated with the placebo effect or strength applied of current to reach defined pain ratings.

Conclusions: Open label placebos might play a role in multimodal analgesic concepts.

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Despite over 50 yr of intense research, achieving adequate pain control remains an unresolved problem.[1–3] Medical pain therapy is often unsatisfactory, and certainly not devoid of side effects, as illustrated by the current opioid crisis.[4] Currently, quick-acting medical therapies are the standard treatments for managing acute pain, but their use is often limited by contraindications and (dose-dependent) side effects.[5–12]

Placebo administration, however, may be a viable, low-risk, low-side-effect treatment option[13] used in various indications[14–17] and settings.[18,19] Pain has become an interesting topic for placebo research[15,18,20] ever since the demonstration that the opiate antagonist naloxone could annul placebo analgesia after wisdom tooth extraction.[21] Current studies suggest that placebos have a clinically significant effect, even when patients and treating physicians are aware that they are receiving/administering a placebo, *i.e.*, an open label placebo. Indeed, open label placebos have been shown to be effective in the treatment of chronic pain,[22] chronic disease,[23] and even allergic rhinitis.[14]

Nonetheless, data regarding open label placebo in acute pain, hyperalgesia, and allodynia are scarce, and its place here unknown. However, open label placebo–augmented add-on or dose-sparing treatment strategies could be of interest in a multimodal analgesia concept, particularly as clinicians have disregarded traditional deception-based placebos in the past. Open label placebo administration releases the treating physician from the ethical dilemma of deceiving the patient with a placebo treatment.[16] Among reservations to the routine clinical use of open label placebos are the limited data about how much time, effort, or patient education is needed for an open label placebo to be effective.

This article is featured in "This Month in Anesthesiology," page 1A. This article has a visual abstract available in the online version. T.S. and J.L. contributed equally to this article.

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In this randomized crossover study, we investigated the effect of open label placebo in healthy adult males on acute pain, hyperalgesia, and allodynia in a well-established pain model.[24] We hypothesized that open label placebo administration leads to a significant reduction of pain measured *via* numeric rating scale, area of hyperalgesia (cm^2), and area of allodynia (cm^2) measured over a time interval of 70 min compared to a control intervention without placebo administration. We additionally hypothesized that the numeric rating scale would be further reduced in participants receiving detailed education and conditioning compared to receiving a short education before placebo administration. Finally, we hypothesized that open label placebo would lead to reduced stress as measured by saliva cortisol.

Materials and Methods

Subjects

This study was approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz, ID 2017-01690, Basel, Switzerland) and conducted at the University Hospital of Basel (Basel, Switzerland) after obtaining written informed consent from each volunteer. The trial was performed in accordance with the Declaration of Helsinki and registered with clinicaltrials.gov (NCT03361579) before recruitment.

Volunteers were recruited by advertisement on the University of Basel's homepage, and inclusion occurred on a "first-come, first-served" basis. Inclusion criteria were healthy adult (18 yr and older) males (American Society of Anesthesiologists Physical Status I to II) with a body mass index between 18 to 25 kg/m^2. Exclusion criteria were recreational drug abuse, regular use of medication having a potential effect on pain sensitization (analgesics, antihistamines, calcium and potassium channel blockers), neuropathy, chronic pain, or neuromuscular or psychiatric disease. Participants were familiarized with the 11-point numeric rating scale for pain (0 = no pain to 10 = severe pain/maximum tolerable pain) and the experimental setup before the first intervention and were financially compensated.

General Study Design

This study was a prospective, randomized, assessor-blinded, crossover study. Specifically, each participant underwent two sessions of induced acute pain. They received no treatment in one session, and intravenous open label placebo (5 ml of 0.9% saline) in the other session (crossover). Intravenous applications was chosen due to possible greater effect size compared to oral application.[25] The order of sessions was randomized. In addition, patients were randomized to receive either a detailed or a 1-min short education on placebos (no crossover).

Exact Procedure of Randomization

Patients were randomized in a two-fold manner using randomization software (randomizer.org). In a first 1:1 simple randomization step of this crossover study, the order of placebo *versus* no treatment was randomized (*i.e.*, no treatment, then placebo, or placebo and then no treatment). In a second step, exactly half of each randomization group was further randomized to receive either a short or a detailed education, again using randomizer.org in a 1:1 simple randomization. This led to four groups of eight patients in this 2 × 2 randomization scheme (fig. 1).

Randomization of all patients was performed by a team member not involved in participant care or outcome assessment. As previously mentioned, the assessor was blinded to the randomization.

The member of the study team responsible for assessing pain, hyperalgesia, and allodynia was blinded to the therapy as well as to the type of placebo education. A 2-week washout period was instituted to attenuate habituation effects.

Placebo Education

Participants randomized to detailed education were provided a placebo education adopted from previous open label placebo studies[17,22] before administration of placebo. The content included (1) data regarding the strength of a placebo effect, (2) the possibility of an autonomous response of the body to a placebo, (3) a statement that, although helpful, a positive attitude toward placebo is not necessary, and (4) a television news report (original English language) with German translation (subtitles) pertaining to open label placebo (excerpted from https://www.youtube.com/watch?v=uv0SuWKZjsI; accessed October 13, 2017). The detailed education was 15 min in duration.

Independent of randomization for education, placebo was administered to all patients with the following sentences (for participants randomized to short education, this was the only education provided):

"I will now inject a placebo in your vein. As you already know from the study documentation, a placebo does not contain an active medical component. We know from recent research that placebos can have a strong positive effect on pain. I am confident that this placebo will substantially reduce your pain as well."

Each participant was cared for by the same person during study inclusion and both interventions.

Experimental Pain Model and Assessment

Intradermal electrical stimulation was used to continually induce pain, secondary hyperalgesia, and allodynia as previously described[24] and as utilized in a number of pain experiments.[26] In brief, two microdialysis catheters with internal stainless steel wires were inserted parallel into the intradermal, volar surface of the forearm for a length of approximately 10 mm and were separated from one another by a 5-mm gap.

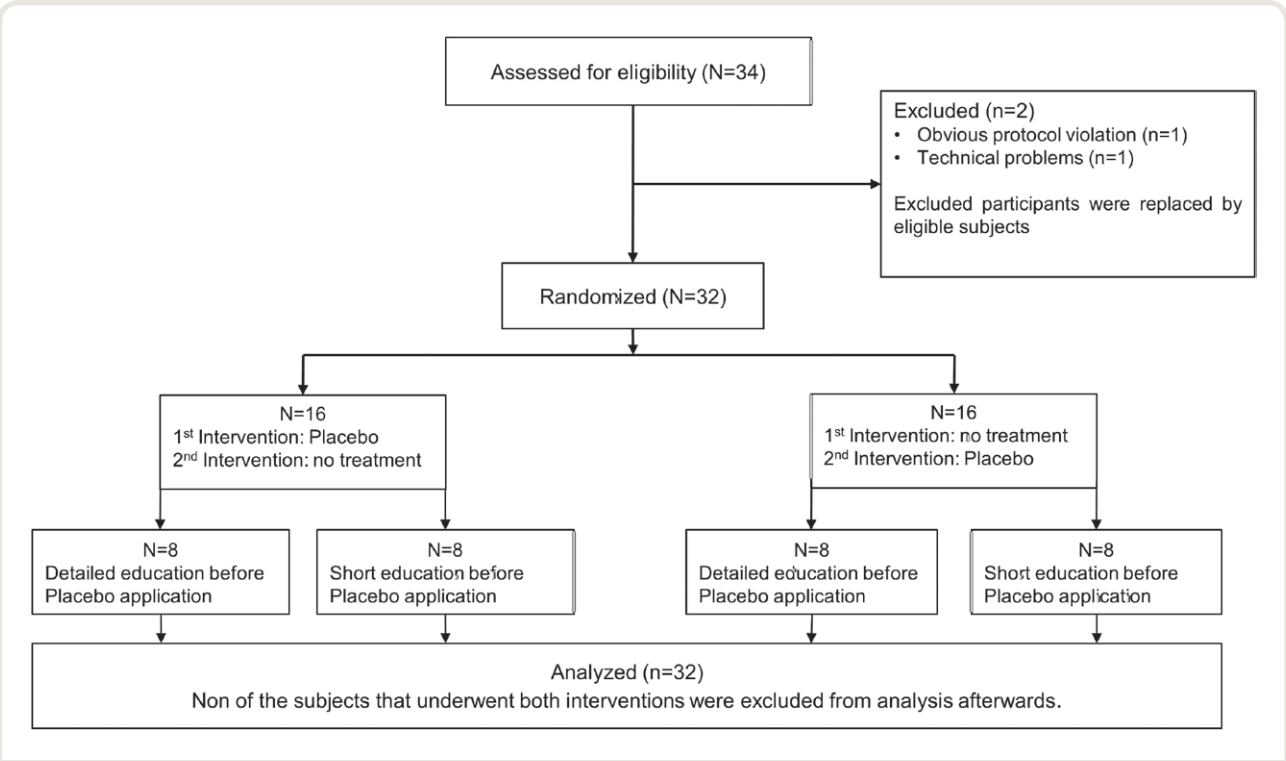

Fig. 1. Patient randomization scheme.

The catheters were filled with 0.9% saline, and a continuous flow of 0.2 μl/min was supplied by a syringe pump (CMA 402, CMA Microdialysis AB, Sweden) to facilitate conduction. The stainless steel wires were attached to an alternating current stimulator (Digimeter S7; Digimeter Ltd., United Kingdom), and monophasic, rectangular electrical pulses 0.5 ms in duration were applied with alternating polarity of 2 Hz. The current was increased to target a pain rating of 6 out of 10 according to the numeric rating scale. After reaching a numeric rating scale of 6, a 15-min time interval for recalibration was set in which the current could be increased to restore a numeric rating scale of 6, thereby compensating for habituation. This final current was kept constant for the next 70 min.

Assessment of Hyperalgesia and Allodynia

Pain, allodynia, and hyperalgesia were assessed every 10 min from minute 30 until minute 100 (fig. 2). Pinprick hyperalgesia was assessed using a 256-mN von Frey filament, and allodynia was determined using a dry cotton swab. Measurements were conducted from a more distal to a more central site along four orthogonal lines (distal, proximal, lateral, and medial). Distal and proximal measures were begun 12 cm from the site of electrical stimulation, whereas the lateral and medial measurements were begun 6 cm from this site. Hyperalgesia and allodynia testing were performed by moving toward the site of stimulation in 0.5-cm increments until the subject reported either increased pain sensations from the von Frey filament (hyperalgesia) or an unpleasant "rougher" sensation from the cotton swab (allodynia). To create an area from these linear measurements, the assumption was made that this field had the shape of an ellipse using the formula ¼ π D · d (D indicates vertical diameter; d indicates horizontal diameter).

Measurement of Saliva Cortisol Concentrations

To control for diurnal variations, all experiments were carried out between 4:00 PM and 7:00 PM. To ensure a noncontaminated measurement, participants were asked (1) to avoid nonprescription medication and alcohol 24 h before the measurement, (2) to refrain from exercise and caffeine at least 2 h before testing, (3) to avoid food that can cause bleeding of the gums, and (4) to not brush their teeth within the 2 h before the testing session.

For saliva collection, a collection swab (Salivette, Germany) was placed in the mouth on the top of the tongue for 2.5 min for each sampling.

Saliva was collected before beginning the experiment after the participant had been sitting quietly for 15 min. In addition, we sampled all participants regardless of randomization at baseline, 30, 60, and 100 min (fig. 2). Saliva probes were directly sent to the laboratory, and concentrations were measured *via* an electrochemiluminescence immunoassay.

Endpoints

Our primary endpoint was the pain response measured by the averaged pain score from minute 30 (time point

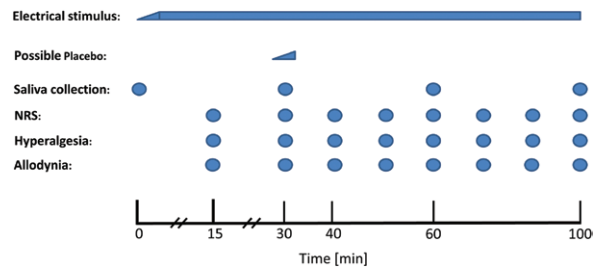

Fig. 2. Schematic illustration of the experimental setup and important protocol steps. NRS, numeric rating scale.

of possible placebo administration) to minute 100 in our experimental setup. The main comparison was the effect of open label placebo *versus* no treatment. We also analyzed the effect of education on this average pain score.

Secondary endpoints were (1) the average areas of hyperalgesia and allodynia over the same time period and (2) saliva cortisol concentrations measured at baseline, 30, 60, and 100 min after pain induction.

Statistical Analyses

For descriptive purposes, patient characteristics are presented as median (first to third quartiles) or mean ± SD, as determined by Shapiro–Wilk test or as a number (percentage). Pain scores, the area of hyperalgesia (cm^2), and the area of allodynia (cm^2) were assumed to be continuous and were measured at specific points in time. In order to determine the area under these curves, we assumed linearity between measurements and multiplied the pain score by minutes spent at that pain score (*i.e.*, measuring a numeric rating scale of 6 at time t and 4 at time t + 15 would yield an area under the curve of 5 numeric rating scale · 15 min or 75 numeric rating scale · min). In response to concerns of the reviewers, the plan of analyses of pain scores was modified. Reported pain scores are calculated as median values of the numeric rating scale, and the area under the curve was calculated for graphical presentation (fig. 3).

For the main hypothesis, we compared the average pain scores from the beginning of placebo administration or no treatment at time 30 min to the end of the experiment at time 100 min using a Wilcoxon signed-rank test. Potential differences in the average areas of hyperalgesia and allodynia were compared analogously, while the effects of education on average pain, average hyperalgesia, and average allodynia were examined by Mann–Whitney—Wilcoxon test. Potential differences in cortisol concentrations by both placebo status and over time were examined by a Wilcoxon signed-rank test. We also explored a possible correlation between baseline cortisol and mean pain, mean hyperalgesia, mean allodynia, and required current to achieve a numeric rating scale of 6 by linear regression.

All testing was two-sided with the level of significance predetermined to be 0.05. All statistical analyses were performed using R 3.4.3 (R Foundation for Statistical Computing, Austria). A sample size of 32 participants was calculated based on an expected difference of 1 point on the numeric rating scale scale and an expected SD of 1 point on the numeric rating scale scale after placebo administration using a paired *t* test with a type I error of 0.05 and power of 0.80. We then adjusted our sample population by 20% for potentially nonparametric data, a nonresponder rate of 20 to 30%, and a dropout rate of 10%.

Outliers were double checked, and none of them could be attributed to a measurement error. Therefore, they were included in the analysis.

Results

Baseline Characteristics

Participants were recruited from October 2017 through February 2018. All participants (n = 32) were white European males aged 18 to 37 yr (median age, 23 yr; first to third quartile: 22 to 26 yr). Mean ± SD body mass index was 23 ± 2 kg/m^2.

Two participants were excluded from the study (one due to consumption of marijuana before the experiment, and one due to technical problems during the intervention). These participants were replaced by newly recruited volunteers. Data of excluded participants were not analyzed. Complete data sets were received for all 32 participants.

Pain Response

Figure 4 (*top panel, two left-most boxplots*) reveals median averaged pain scores to be significantly lower during open label placebo compared to no treatment (4.0 [first to third quartile, 3.2 to 4.9] *vs.* 5.1 [first to third quartile, 4.7 to 5.4, $P = 0.001$]). This is a 21% reduction. Figure 3 (*top panel*) shows that while pain decreased over the course of the experiment, a greater and stable decrease occurred with placebo upon administration (time 30 min). Absolute values for every measurement point are shown in this figure.

Hyperalgesia and Allodynia Response

Re-examining figure 4 (*bottom two panels, two left-most boxplots*) shows that similar to median averaged pain scores, median averaged hyperalgesia, and median averaged allodynia were significantly lower during placebo treatment than during the no treatment intervention (30 cm^2 [17 to 47 cm^2] *vs.* 55 cm^2 [42 to 68 cm^2]; $P = 0.003$; and 24 cm^2 [11 to 39 cm^2] *vs.* 45 cm^2 [31 to 62 cm^2]; $P = 0.007$, respectively). This corresponds to reductions of 47%. Similar to pain, figure 4 (*bottom panels*) shows the reduction also began with administration of placebo and lasted throughout the experiment.

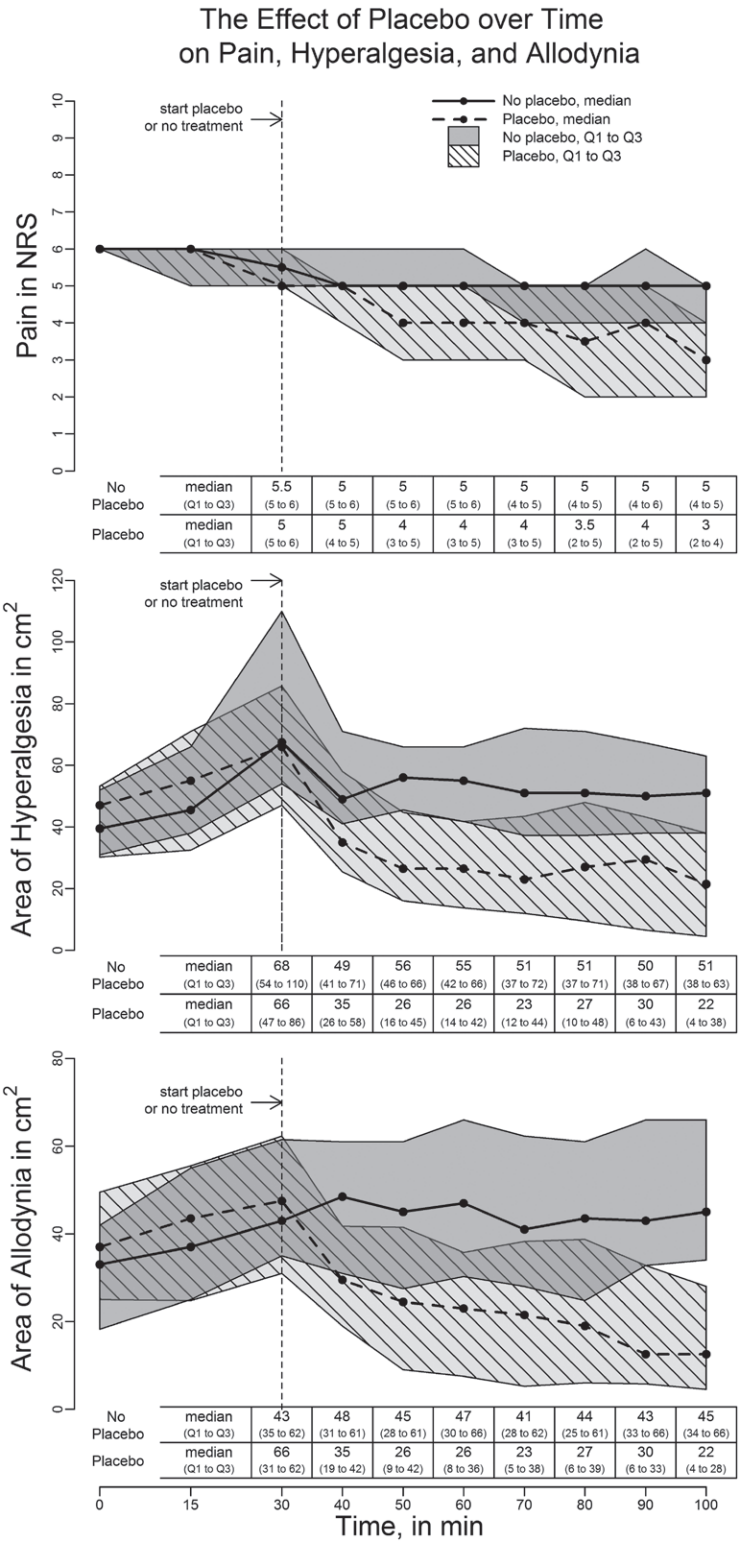

Fig. 3. The effect of placebo over time on pain, hyperalgesia, and allodynia during the entire experiment. The lines show the median values, and the areas correspond to the interquartile ranges. Median values with first and third quartile (Q1 to Q3) on specific time points are indicated on the bottom of the panels (included participants N = 32). NRS, numeric rating scale.

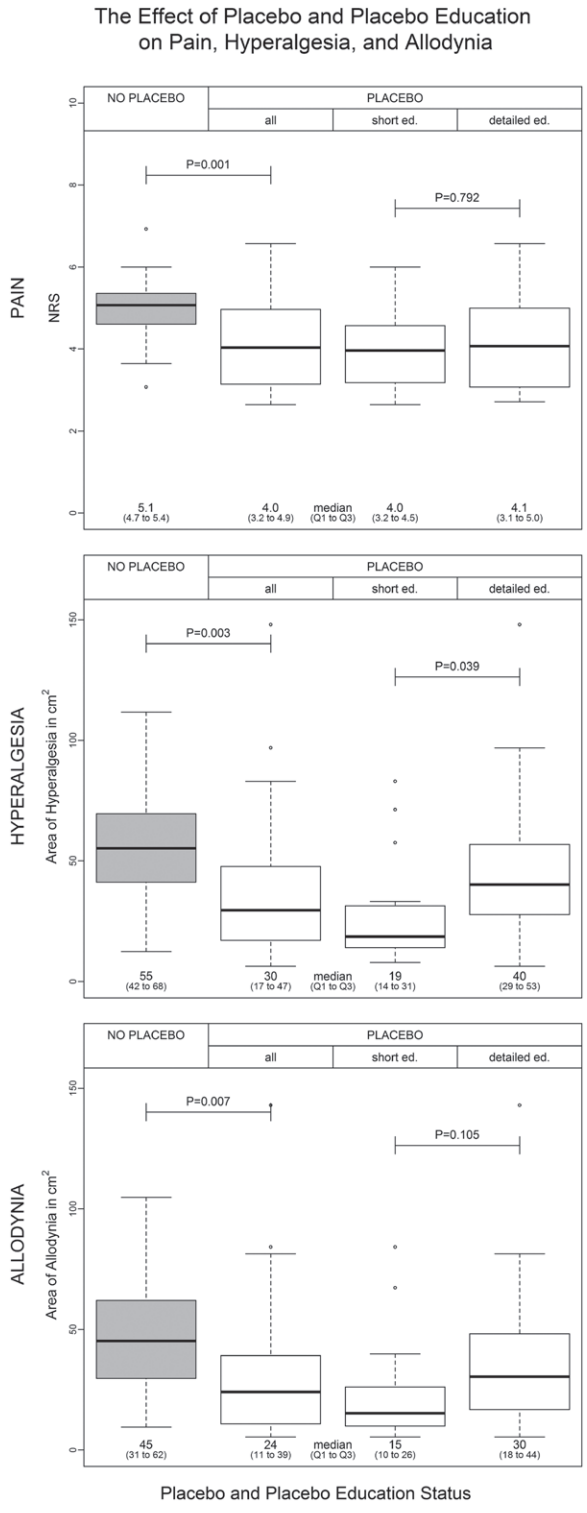

Fig. 4. Box plots for median averaged pain scores, median averaged areas of hyperalgesia (cm^2) and allodynia (cm^2) for no placebo *versus* placebo treatment and education (ed.): short *versus* detailed. *P* values of main comparisons are provided. Median values with first and third quartile (Q1 to Q3) are listed on the x axis (included participants N = 32). NRS, numeric rating scale.

Effect of Education on Outcome Parameters

The extent of the placebo effect on pain ratings was equally strong in the detailed and short form education group ($P = 0.792$; *two right-most boxplots* in fig. 4). A possible effect of the extent of placebo education on hyperalgesia (19 cm^2 [14 to 30 cm^2] *vs.* 40 cm^2 [29 to 53 cm^2]; $P = 0.039$) and allodynia (15 cm^2 [10 to 26 cm^2] *vs.* 30 cm^2 [18 to 44 cm^2]; $P = 0.105$) may exist with higher values in the group receiving detailed education. A test of the effects of education on cortisol concentrations was not applied due to the fact that cortisol dropped below detectable concentrations in the majority of participants during the experiment.

Saliva Cortisol Response

Saliva cortisol concentrations were significantly reduced when measured after 60 ($P < 0.001$) and 100 min ($P < 0.001$) compared to measurement before pain induction and before possible placebo administration. We could not demonstrate a significant influence of placebo administration on saliva cortisol concentrations during the experiment. After 60 and 100 min, saliva cortisol concentrations were 3 mg/dl or lower (3 mg/dl was the lower detection limit of the measurement method) in a majority of participants (26 first session; 22 s session; fig. 5).

Baseline cortisol concentrations did not correlate with median averaged pain ($P = 0.996$), median averaged hyperalgesia ($P = 0.395$), median averaged allodynia ($P = 0.395$), and current required to achieve a numeric rating scale of 6 after adaptions ($P = 0.641$).

Discussion

In this prospective, assessor-blinded, crossover trial of induced pain in healthy participants, we found open label placebo to significantly reduce pain, hyperalgesia, and allodynia. We did not find a benefit of detailed *versus* short placebo education. Detailed education may have, in fact, increased measures of central sensitization.

Clinical Relevance and Contribution of Our Study to the Existing Literature

First, these data expand upon previous trials examining open label placebo and pain. A randomized trial by Carvalho *et al.* examining a cohort of 97 adults suffering from lower back pain first showed a clinically significant effect of open label placebo treatment added to the usual treatment compared to the usual treatment alone (pain reduction of 1.5 *vs.* 0.2 points on a numeric rating scale).[22] Locher *et al.* investigated the open label placebo effect in an acute pain setting with a model measuring heat tolerance in 160 healthy adults. In this randomized trial, the effect on subjective pain ratings was significant, but due to the short exposure time in the model used, no conclusions about a clinical effect could be made.[17]

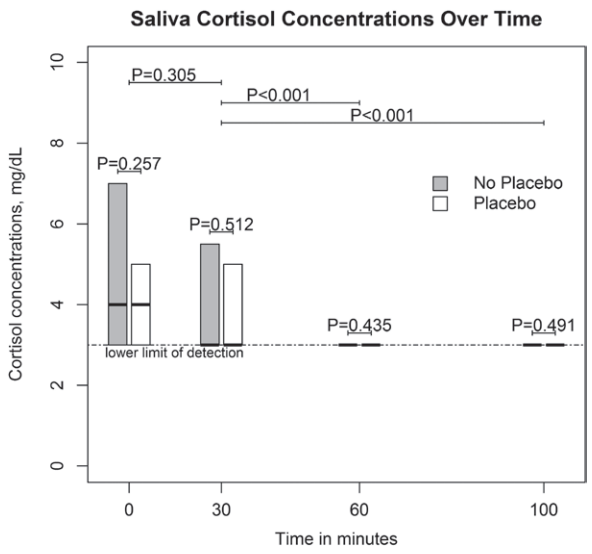

Fig. 5. Box plots depicting saliva cortisol concentrations over time. Cortisol concentrations after 60 and 100 min were mostly blow the lower limit of detection. *P* values of the main comparisons are provided (included participants N = 32).

The observed pain reduction due to placebo in our study was of statistical relevance and may also be clinically relevant (21% reduction, 1 numeric rating scale point). This was similar for hyperalgesia and allodynia (47% for both). More importantly, the placebo effect lasted in full strength throughout the measurement period (70 min). Thus, the effect is robust against an ongoing stimulus of acute pain.

Second, we examined the extent to which placebo education required elaboration, which is an important consideration in a clinician's decision to employ a given therapy. Most studies pertaining to open label placebo have been based on providing transparent education about the placebo effect.[17,22,23,27] Schaefer *et al.* could show that a placebo education is important for the subjective symptom interpretation, but open label placebos have equal effectiveness for the objective symptoms of allergic rhinitis with or without education.[14] The study by Locher *et al.* corroborates these findings for the subjective intensity and unpleasantness ratings for heat pain tolerance.[17] In the recent published studies of open label placebo treatment for various conditions, participants received a relatively detailed placebo education.[17,22,23,28]

As a combination of an objective biochemical processes (nociception) and emotional processing,[29] pain is a complex entity. As such, the role of placebo education should not be neglected. Our study shows that a short form of education is sufficient and potentially beneficial. For both clinical and routine implementation, these are important results suggesting that short education suffices, the placebo effect is lasting, and deception is not required.

Third, data about placebos and central sensitization embodied by hyperalgesia and allodynia are sparse. It is important to include these modalities, because central sensitization is clinically neglected, but is exceedingly common after surgery and has been linked to persistent and chronic pain.[30,31]

Summary of Possible Placebo Mechanisms

Clinical implementation of placebo use has identified three key points for optimal analgesia: patient expectation,[32–35] physician–patient communication,[36,37] and conditioning of the patient.[13,38,39]

One of the most interesting findings in our study is the strong effect of placebo on the pain modifying modalities, hyperalgesia and allodynia. Hyperalgesia can be further divided into primary hyperalgesia, due to lower thresholds of peripheral Aδ and C-fibers, and secondary hyperalgesia, due to changes in the spinal cord and higher brain areas. Our model mainly tests for secondary hyperalgesia *via* central sensitization, which typically manifests in tactile allodynia and secondary hyperalgesia. In our setting, it is speculative whether homosynaptic and/or heterosynaptic potentiation are mainly responsible for increasing postsynaptic depolarization, inducing an increased output from the dorsal horn neuron leading to central sensitization.[30,40] But known mechanisms of placebo analgesia primarily affect central processing of pain. This is known for psychologic factors (*i.e.*, expectation, communication, and conditioning) and for the endogenous opioid[39] and cannabinoid[41] systems, which are examples of the neuroendocrine basis of placebo analgesia.[42] These could be possible explanations for the strong response regarding hyperalgesia and allodynia in our study population. While we are not able to conclusively define the responsible pathways, the clinical effect remains impactful.

From Experiment to Bedside

Transfer of results generated in a model including healthy volunteers to actual patients is complex, and open questions must be addressed. First, electrical skin stimulation does not simulate deep somatic or visceral inputs in patients. Although the results of open label placebos for the treatment of chronic visceral pain syndromes[23,43] are promising, little is known about placebos and acute (postoperative) visceral pain. Second, our model does not assess primary hyperalgesia, a modality connected to acute postoperative pain. The effect of open label placebo on primary hyperalgesia would be of great interest, but requires another experimental setting. Third, to define the adequate timing and indication for open label placebos in clinical practice. The authors of the current study suggest open label placebos as potential dose extenders (savers) for implementation in a multimodal pain concept (*e.g.*, in a postoperative setting) to boost and extend effects of a given verum. Colloca *et al.* showed the dose extending properties of placebos for

pain killers.[13] Nonetheless, the effect on acute pain remains unclear.

Saliva Cortisol

Altered cortisol concentrations are associated with acute stress and pain conditions.[44,45] Consistent with the procedures incorporated by Dickerson and Kemeny,[45] we decided to measure salivary cortisol as a biologic parameter for stress and pain response. Saliva concentrations of cortisol are reliable and highly correlated with plasma concentrations,[46] thus representing a less reactive and less invasive but reliable measure of neuroendocrine stress and pain response.

Cortisol is present in its unbound active form in saliva, and its concentration is independent of saliva flow rate.[44] Previous research shows that peak concentrations of saliva cortisol can be expected 30 min after stressor onset.[45] Concentrations return to baseline at a similar rate after the stressor stops.

Furthermore, the fact that we did not detect a difference in saliva cortisol concentrations may be due in part to the method (electrochemiluminescence immunoassay), which is not able to reliably measure concentrations less than 3 mg/dl. On the other hand, we interpreted the higher cortisol concentrations before pain induction and after 30 min of constant pain due to stress of the participants on account of the unknown situation and the expectation of pain during the second session. In our opinion, it does not make sense to use a more precise method to detect concentrations less than 3 mg/dl, which are already within the reference concentrations for cortisol.[47] If stress hormones are used as a marker for pain and pain reduction, elevated concentrations in nonresponders should be expected. In our study, saliva cortisol concentrations were not associated with maintenance or reduction of pain.

Strengths and Limitations

This prospective, assessor-blinded, randomized crossover study has a number of strengths, including its design and the implementation of an established pain model. However, some important limitations need to be addressed.

We did not control for taking steroids before or during the study. However, a possible influence on the results is not expected, due to the fact that 29 of the 32 participants were classified as American Society of Anesthesiologists Physical Status I. This excludes medication use in the vast majority of participants.

We only conducted measurements for 1 h. This period is too short to fully establish clinical effectiveness. Second, we examined pain in healthy participants, and it is unclear whether or not hyperalgesia and allodynia are the same in patients. Some data, however, have suggested that placebo analgesia in clinical settings is even greater because of the increased desire for pain relief in patients compared to healthy adults.[48,49] Third, our study only included young men. This limits external validity to a certain degree, and is a significant limitation of our investigation. A 2017 review article by Vambheim and Flaten[50] reports on the sex differences in reaction to placebo. In general, women are less sensitive to the placebo effect. Women were found to respond less to verbal suggestions but more to detailed education. It is therefore possible that our experimental design and participant collective overrate the placebo effect. Follow-up investigations including a broader spectrum with respect to sex, age, ethnicity, and cognitive function need to be performed.

Based on our results and those of others, we suggest that future clinical studies focus on (1) the additive effect of placebo in a regimen of multimodal therapy, and (2) the effect of placebo on older or high-risk patients of both sexes.

Conclusions

Open label placebo can reduce acute pain, hyperalgesia, and allodynia in healthy male participants. While placebo education is an important component in the complex entity of pain, a short education seems to suffice. Based on our study and those of others, open label placebos, embedded in a multimodal treatment approach, could play an important role in the clinical management of acute pain in the future. Nonetheless, more research in broader collectives regarding age, sex, and combination of drugs and placebos is essential to gain a better understanding of how placebos can support the effectiveness of drugs and psychosomatic interventions to treat acute pain.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: tobias.schneider@usb.ch. Raw data available at: tobias.schneider@usb.ch.

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