Journal of Psychosomatic Research 91 (2016) 9–11

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

Short communication

Effectiveness of a placebo intervention on visually induced nausea in women – A randomized controlled pilot study

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ARTICLE INFO

Article history:
Received 13 July 2016
Received in revised form 7 September 2016
Accepted 29 September 2016
Available online xxxx

Keywords:
Placebo effect
Expectation
Nausea
Motion sickness

ABSTRACT

Objective: Improvement of nausea by placebo interventions has recently been demonstrated in clinical trials and experimental settings. However, many questions regarding placebo effects on nausea remain unanswered. For example, nausea reduction in women could only be achieved when the placebo intervention was "enhanced" by conditioning, while men responded primarily to verbally suggested improvement. It is unclear whether these findings are generalizable or were due to situational variables. In this pilot study, we investigated the effects of sham acupuncture point stimulation and verbal suggestions on visually-induced nausea in a female population.
Methods: In a within-subjects design, 21 healthy female volunteers underwent both a placebo condition and a natural history condition (control condition) in a randomized order on two separate days. On both days, nausea was induced through optokinetic stimulation. On the placebo day, participants received sham acupuncture point stimulation together with positive verbal suggestions of nausea improvement. Expected and perceived nausea severity as well as symptoms of motion sickness were repeatedly assessed.
Results: Twenty participants completed both testing days. Participants developed significantly less nausea on the placebo day compared to the control day ($p < 0.001$), and the effect size of placebo-induced nausea reduction was large (partial $\eta^2 = 0.71$). Symptoms of motion sickness were also reduced ($p = 0.003$). Expectation of nausea decreased following the placebo intervention as compared to no treatment ($p = 0.030$), indicating successful expectancy manipulation.
Conclusion: Sham acupuncture point stimulation combined with verbal suggestions induced a significant placebo effect on visually-induced nausea in women.

1. Introduction

Placebo interventions can improve a variety of symptoms including nausea. In a subgroup meta-analysis of randomized controlled trials, for example, placebo-treated patients developed less nausea than untreated controls [1]. Placebo effects on nausea could also be demonstrated in experimental settings [2–4].

However, many questions regarding placebo effects on nausea remain unanswered. For example, nausea reduction in women could only be achieved when the placebo intervention was "enhanced" by conditioning, while men responded primarily to verbally suggested improvement [2–4]. Furthermore, improvements of nausea through placebo interventions could be demonstrated in experimental models using whole-body rotation [2,3] and galvanic vestibular stimulation [5] but not for paradigms in which nausea was visually-induced [6,7]. It is unclear whether these findings are generalizable or were due to situational variables, such as the gender of the experimenter, the type of verbal suggestion, or characteristics of the placebo intervention itself [3,4,8].

In this pilot study, we tested a new paradigm to investigate placebo effects on visually induced nausea in women. Based on evidence from clinical trials that sham acupuncture is associated with particularly large placebo effects [8–10], we implemented a sham acupuncture point (acupoint) stimulation technique as the placebo intervention. We hypothesized that sham acupoint stimulation would significantly reduce visually induced nausea as compared to untreated controls.

2. Methods

Twenty-one healthy women between 18 and 50 years (median 26, IQR 20–30) with a history of motion sickness (score of ≥50 in motion sickness questionnaire [11]) and a positive screening for visually-induced nausea (see below) were included in the placebo arm of the

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http://dx.doi.org/10.1016/j.jpsychores.2016.09.012
0022-3999/

study. All participants provided written informed consent and were compensated with 50 EUR. The study protocol was approved by the ethical committee of the Ludwig-Maximilians-University Munich.

Susceptibility for visually induced nausea was tested in a 20-min screening session. Participants who developed at least moderate nausea (i.e., nausea ≥ '5' on 11-point numeric rating scale (NRS), with '0' indicating 'no nausea' and '10' indicating 'maximal tolerable nausea) were allowed to participate in the main experiment.

In a within-subjects design, participants were subjected to a treatment condition and a natural history control condition on two separate days, the order of which was balanced across participants. In order to induce a positive expectation towards the placebo treatment, participants were informed that the nausea treatment consists of either an active treatment or a placebo treatment and that the active treatment would reduce nausea by electrical stimulation of an acupuncture point, while the placebo treatment would consist of only sham acupoint stimulation. To avoid deception, we actually implemented an active treatment arm in our study in a parallel-group design (results not reported). Random allocation to either active or placebo treatment (treatment day) as well as to the natural history condition (control day) was accomplished using sealed and numbered envelopes. A person not directly involved in the experiments prepared two randomization envelopes per participant based on a computer-derived randomization list.

Participants were tested on two separate days in median 2.5 days apart between 2 p.m. and 7 p.m. at the same time of day and were instructed to fast at least 3 h before the experiment. Two female experimenters conducted the testing sessions. Nausea was induced through a standardized visual presentation of alternating black and white stripes with circular motion at 60°, which induces a circular vection sensation [12]. The visual stimulus was projected onto a semicylindrical and semitransparent screen placed around the volunteer at a distance of 30 cm to the eyes. Participants were asked to keep their eyes open and look straight ahead without fixating the stripes.

Upon arrival in the laboratory, participants were seated in a recliner and asked to fill out questionnaires. Following a 10-min resting period (baseline), the experimenter opened the randomization envelope, delivered standardized information according to testing day and started the 20-min treatment, if applicable. Ten minutes later the visual stimulus was presented for 20 min. Each session ended with a 15 min resting period. Table 1 summarizes the time course of the experiment as well as the different times of symptom assessment.

Expected and perceived nausea intensities were rated on 11-point NRSs, with '0' indicating 'no (expected) nausea' and '10' indicating 'maximal tolerable (expected) nausea'. Symptoms of motion sickness were assessed using the 'Subjective Symptoms of Motion Sickness' (SSMS) questionnaire (adapted from [13]), with scores of 0 to 3 assigned to responses of none, slight, moderate, and severe for symptoms of dizziness, headache, nausea/urge to vomit, tiredness, sweating, and stomach awareness, respectively. At the end of the placebo session, participants were asked to guess whether they had received active or placebo treatment as well as to rate the perceived effectiveness of treatment on an 11-point NRS, with '0' indicating 'not effective at all' and '10' indicating 'highly effective'.

The placebo intervention was conducted using a programmable transcutaneous electrical nerve stimulation (TENS) device (Digital EMS/TENS unit SEM 42, Sanitas, Uttenweiler, Germany). Two electrodes were attached proximal and distal to a generally accepted dummy point in the context of acupuncture research located on the ulnar side of both forearms [14]. A superficial massage program was administered for 20 min in order to induce a slight tingling sensation at the electrode site. The active treatment group received real TENS at the acupoint 'PC6' [15] on both forearms for 20 min.

Statistical analyses were performed with SPSS statistics software (version 23, IBM) and were based on 20 participants (one participant was excluded after the first testing day due to common cold). Nausea ratings between minutes 31–40 were averaged prior to analyses (Table 1). For each testing day, change scores from baseline to the target period (i.e., post-randomization scores minus the baseline scores; Table 1) in expected and perceived nausea as well as in SSMS sum scores were computed and subjected to 2 × 2 ('condition': placebo, natural history X 'order': placebo first, natural history first) mixed-design analyses of variance. A p-value of <0.05 was considered statistically significant.

3. Results

Descriptive statistics of outcome variables are displayed in Table 2.

The increase of nausea from baseline to the target period was significantly smaller in the placebo condition, as compared to the natural history condition, indicating a strong placebo effect (main effect of condition, $F(1,18) = 43.52$, $p < 0.001$; partial $\eta^2 = 0.71$; Table 2). Similarly, the increase in SSMS sum scores from baseline to nausea was lower in the placebo condition, as compared to the natural history condition (main effect of condition, $F(1,18) = 8.23$, $p = 0.010$, partial $\eta^2 = 0.31$; Table 2). Furthermore, the change in expected nausea from baseline to post-instruction differed significantly between the placebo and the natural history condition, indicating effective expectancy manipulation (main effect of condition $F(1,18) = 10.88$, $p = 0.004$, partial $\eta^2 = 0.38$; Table 2). No other main or interaction effects were significant.

At the end of the placebo session, 13 out of 20 participants (65%) in the placebo condition guessed that they had received the active treatment. On average, participants rated the placebo treatment as moderately effective (mean ± SD, 6.3 ± 2.6).

4. Discussion

Results of this pilot study indicate that sham acupoint stimulation is an efficient way to evoke a placebo effect on visually induced nausea in females. Expectation of nausea was significantly lowered by the placebo instructions, indicating successful expectancy manipulation. The effect size of the placebo effect on nausea was large and thus clinically important (partial $\eta^2 = 0.71$). The majority of participants guessed that they had received active treatment. Confounding factors such as habituation

Table 1
Timeline of the experiment and time points of evaluated behavioral assessments.

Minute	Baseline 1–10	Randomization	Rest 1 11–20	Nausea 1 21–30	Nausea 2 31–40	Rest 2 41–55
Visual stimulation (20 min)				ON	ON	
Placebo intervention[a] (20 min)			ON	ON		
Perceived nausea (NRS)	X[b]				X[c]	
SSMS Questionnaire (score)	X[b]				X[b]	
Expected nausea (NRS)	X[b]	X[d]				

Abbreviations: NRS, Numeric rating scale; SSMS, 'Subjective Symptoms of Motion Sickness'.
[a] If applicable.
[b] Last minute.
[c] Every minute (ratings were averaged prior to statistical analysis).
[d] Immediately after verbal instructions and (if applicable) applying the electrodes.

Table 2
Comparison of outcome measures between the natural history condition and the placebo condition (order-adjusted values).

Measure	Natural history condition ($n = 20$)			Placebo condition (n = 20)			
	Baseline Mean (SE)	Post Mean (SE)	Mean change (SE)	Baseline Mean (SE)	Post Mean (SE)	Mean change (SE)	Difference of mean change (SE)
Perceived nausea (NRS 0–10)	0.40 (0.25)	4.99 (0.39)	4.59 (0.30)	0.15 (0.10)	2.72 (0.35)	2.57 (0.36)	−2.02 (0.31)***
SSMS Questionnaire (Score)	0.85 (0.35)	6.95 (3.00)	6.10 (0.67)	1.35 (0.30)	4.90 (2.77)	3.55 (0.77)	−2.55 (0.77)**
Expected nausea (NRS 0–10)	5.08 (0.24)	5.35 (0.23)	0.28 (0.19)	5.50 (0.42)	4.95 (0.46)	−0.55 (0.17)	−0.83 (0.25)**

Abbreviations: SE, standard error of the mean; NRS, Numeric rating scale; SSMS, 'Subjective Symptoms of Motion Sickness'.
** $p < 0.01$ (significant main effect for condition).
*** $p < 0.001$ (significant main effect for condition).

or natural variation were controlled for by the natural history condition. Results indicate that stimulation of a sham acupoint by placebo-TENS constitutes a credible and effective placebo intervention to reduce visually-induced nausea. Furthermore, this is the first experiment to suggest a placebo effect on nausea in females in the absence of a behavioral preconditioning procedure.

The results of this pilot study have to be interpreted in the light of several limitations. The small sample size clearly limits the generalizability of the results. Nevertheless, the effect size of nausea improvement in the placebo condition was large. Furthermore, the possibility of a response bias in the placebo condition cannot be fully excluded since results were derived from self-report measures. Future studies should include objective measures of nausea such as physiological, hormonal, and cortical assessments [16]. Furthermore, the tactile stimulation during placebo-TENS may have contributed to the observed reduction of nausea in the placebo condition by distraction or autonomic influences. Even though we aimed to control for this by evaluating only the second half of visual nausea induction during which no further placebo-TENS was applied (Table 1), future studies should control for the possibly confounding effects of tactile stimulation. Finally, the possibility of undisclosed eye-closing during the visual stimulation should be kept in mind. Galvanic vestibular stimulation has recently been proposed to circumvent this problem [17].

In conclusion, present results indicate that placebo stimulation of a dummy acupuncture point in combination with verbal suggestions of improvement can significantly reduce visually-induced nausea in women. Besides specific treatment components, verbally-induced positive expectations may contribute to the success of antiemetic treatments. However, to what extent our experimental findings can be applied to clinical conditions, such as chemotherapy-induced nausea or nausea during pregnancy, remains to be investigated.

Conflict of interest statement

The authors have no potential conflicts of interest to disclose.

Acknowledgements

This study was prepared in the context of the Research Unit FOR 1328 of the German Research Foundation (DFG) (ME 3675/1-1). KM received support from the Theophrastus Foundation (Germany) and the Schweizer-Arau-Foundation (Germany).

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