Review Article

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Limiting the Placebo and Hawthorne Effect In Periodontal Clinical Trials: Current Concepts and Future Directions

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ABSTRACT

Background: The primary aim of this review was to assess effects of placebo interventions in periodontal clinical trials. The study also sought to examine whether trials have included special strategies to identify placebo responders and differences in outcomes between placebo and control groups.

Materials and Methods: The MEDLINE bibliographic database and the PubMed Central (PMC) digital repository were searched for English language articles. Assessment of study quality focused on two key domains; results attributable to Hawthorne effect or placebo effect and study design options to identify placebo responders and to lower the placebo effect. Allocation to comparison groups, instances of auxiliary care apart from treatments under evaluation, assessment of outcomes were also assessed.

Results: The MEDLINE search yielded 6 articles and the PMC search yielded 16 articles. Additional 2 articles were found from references from the above articles. In many trials, the terms 'placebo effects" and 'Hawthorne effect" were used without distinction on whether the clinical improvement in a group of patients is attributable to the fact of being under study or because of the belief in the material being used. In periodontics, there are a paucity of trials which have effectively filtered out the "placebo responders" *i.e.* subjects in which the clinical evidence is overshadowed by the placebo effect.

Conclusion: The terminology used to describe the placebo effect or Hawthorne effect is inconsistent and is a matter of intensive debate. The biggest grey area for a researcher or an author is the lack of standard guidelines towards using terms such as placebo and Hawthorne effect. Even after recognizing these effects, there is clearly a paucity in tools predicting the degree and effects of these responses.

Keywords: Hawthorne effect, placebo, periodontal disease.

INTRODUCTION

The purpose of a clinical trial is to determine whether a treatment is effective and safe enough through a prospective study comparing the effect of an intervention against a control.[1] The control can be a placebo control, no-treatment control, positive/active control or an historical control.[2,3] Hence, a treatment modality can be considered as effective if it shows superiority to known effective treatment ("active control"), superiority over a placebo or at least shows non-inferiority when compared to an active control.[4] Of all the controls, placebo controls offer a clear reference point and

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they increase the likelihood of attaining statistical significance with a smaller sample size.[5]

Historically, a placebo was any medicine given more to please than benefit the patient. However, as reviews of related effects on placebos in human trials began to surface, placebos were shown to deliberately have an effect on experimenters and were unknowingly known to influence components of various diseases under study.[6] The origin of these effects were unknown, but as of now, a placebo is still defined as a simulated or otherwise medically ineffectual treatment for a disease or other medical condition intended to deceive the recipient.[5, 6] Various accounts of subjective and objective effects gave rise to the term "placebo effect" which is a beneficial physical or psychological change in a person resulting from conscious or non-conscious "beliefs" unaided by any medically active pill or procedure.[7] A treatment modality is said to have a placebo effect if a patient's response to treatment depends positively on his expectations about the value of that treatment.[7, 8]

The term, placebo effect is sometimes used synonymously with the term 'Hawthorne effect"; however, there are considerable differences between these two.[9, 10] Some clinical trials in periodontics have now recognized that subjects realize by way of side effects, investigator behavior and treatment mechanisms, that they have been assigned to the treatment group and are receiving the actual intended treatment.[11, 12] However, searching for the phrase "placebo effect periodontitis" leads to a lot of duplicate and indistinguishable collisions with the phrase "placebo". The Hawthorne effect is not the only phenomenon related to the placebo effect. The *Pygmalion effect* is the phenomenon when greater experimenter expectation is placed upon a subject group, the performance of the group shows an exaggerated improvement than expected[13] *(figure 1)*. The *John Henry effect* is an extreme form of the Hawthorne effect; it is when a supposedly control group, that gets no intervention, compares themselves to the experimental group and through extra effort gets the same effects or results.[14] A *Halo effect* is an extended form of the Hawthorne effect; it is when the participants perform differently at different stages of the trial because of the novelty of the "treatment" and various factors which may change their expectations.[15] Interestingly, the above mentioned terms find almost no mention in periodontal literature.

The primary aim of this review was to assess effects of placebo interventions in periodontal clinical trials. The study also sought to examine whether trials have included special strategies to identify placebo responders and differences in outcomes between placebo and control groups.

MATERIALS AND METHODS

Sources of Information: To identify relevant articles for this review, the MEDLINE bibliographic database and the PubMed Central (PMC) digital repository were searched by using the following phrases alone or in combination: "Periodontitis Placebo Effect", "Periodontitis Hawthorne Effect", "Periodontal Therapy Placebo Effect" and "Periodontal Therapy Hawthorne Effect". Additionally, the reference list of the most relevant papers was examined to identify potential additional articles. We identified 564 abstracts that were assessed for suitability as per the Population, Intervention, Comparator, Outcome (PICO) format.

Eligibility Criteria: The following were the inclusion criteria: 1) English language; 2) human clinical trials; 3) articles reporting on the detection and probable effects of placebo effect in a trial. Manuscripts *not* containing the phrases "hawthorne effect" or "placebo effect" were excluded.

PICO Criteria

Population: Participants of any age receiving periodontal or oral-hygiene therapy as a part of a clinical trial were evaluated. ***Intervention:*** Trials involving an appropriately designed experimental approach based on randomized allocation to an intervention were considered. ***Comparison:*** The attribution of a clinical change to placebo effect in studies having a control group receiving no or different intervention. ***Outcome:*** Outcomes immediately resulting from the placebo effect during the intervention were evaluated.

Data Collection: 564 abstracts that were assessed for suitability by two panel members (RVC and SN). The placebo and total sample size, the type of trial used, the number of treatment arms, the types of treatment and evaluation, the unusual outcome

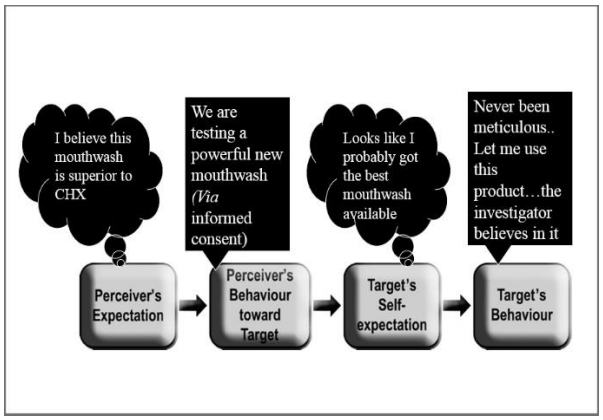

Fig 1: Pygmalion effect; a hypothetical example on how investigator expectation can affect subject behaviour.

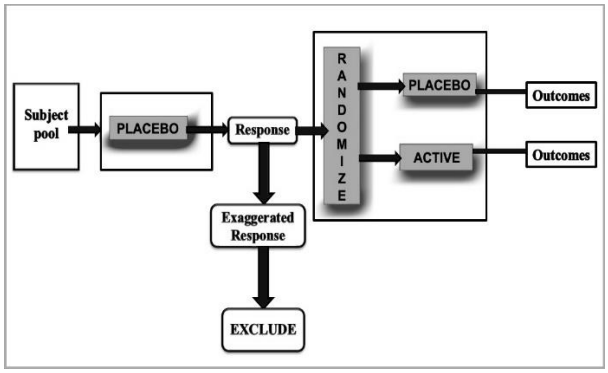

Fig 2: A placebo lead-in trial enables identification of participants showing exaggerated placebo response who are subsequently excluded from the trial.

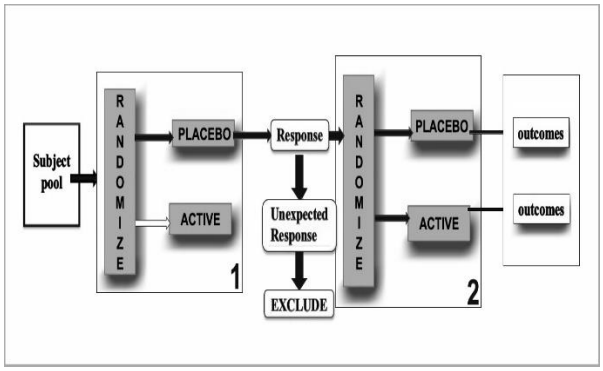

Fig 3: The Sequential parallel comparison design (SPCD) has two specific stages; 1: the initial stage compares the drug and placebo, as in a parallel design and generates a pool of placebo non-responders. 2: The succeeding stage, compares the drug and placebo, as in a parallel design, but utilizes only the placebo non-responders.

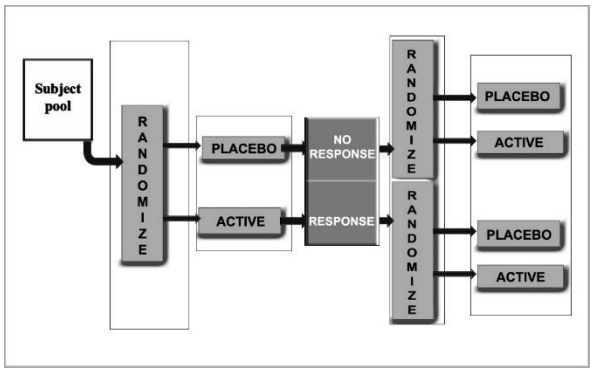

Fig 4: In the Two Way Enriched Design (TED), patients are initially randomized between drug and placebo groups. Later, placebo non-responders and drug responders are re-randomized between drug and placebo groups.

attributed to placebo effect and the study duration were examined in each study.

Quality Assessment

Assessment of study quality focused on two key domains; results attributable to Hawthorne effect or placebo effect and study design options to identify placebo responders and to lower the placebo effect. About 85% of the studies which have mentioned the word "placebo effect" without attributing its effect to an outcome were summarily rejected. Allocation to comparison groups, instances of auxiliary care apart from treatments under evaluation, assessment of outcomes were also assessed. Identified studies were independently assessed by two non-blinded reviewers in a customized data collection chart. Discrepancies were resolved by discussion between the lead authors.

RESULTS

The MEDLINE search yielded 6 articles and the PMC search yielded 16 articles (excluding two of which were also found in MEDLINE). Additional 2 articles were found from references from the above articles. In many trials, the terms 'placebo effects" and 'Hawthorne effect" were used without distinction on whether the clinical improvement in a group of patients is attributable to the fact of being under study or because of the belief in the material being used. Meta-analysis was not carried out as placebo effects were seen in primary and secondary outcomes in different trials contributing to

significant heterogeneity among various oral-hygiene, non-surgical and hypersensitivity studies.

Results attributable to Hawthorne effect/Placebo effect

Table 2 summarizes the variables and effects susceptible to the placebo effect. A plethora of toothbrushing and oral hygiene studies[16] have attributed the initial reductions in the plaque[17] and gingivitis scores[18] and overall treatment benefits to placebo effect[19] *(Table 2)*. Studies also mention about "attention bias[20]", "behavioural change[21, 22]" and an "initial novelty effect[23]" as contributing to placebo effect. Subjects who were aware that they are study participants[11, 21, 22] can show placebo effect affecting the interpretation of the results. Interestingly, in studies on dentinal hypersensitivity (DH), the placebo response has been shown to play a significant role in clinical trials[23] with the perception of pain affecting the stimulus and the placebo response as well[24] *(Table 2)*. A systematic review on the efficacy of desensitizing products has stated that pain experienced and reported due to DH is subjective in nature and discrepancies in clinical trials involving DH prevalence can result due to both the Hawthorne/placebo and non-placebo effects throughout the duration of the study.[25] Of particular importance is the ambiguity in using the terms "placebo effect" and "Hawthorne effect". A placebo response is a change in a subject's condition attributable to the symbolic import of a treatment rather than a specific pharmacologic or physiologic property whereas the Hawthorne effect is any positive effect attributable to a behavioural change due to an awareness of being observed.[9, 10] While some studies correctly attribute the behavioural changes in the study to Hawthorne effect,[22] studies which have utilized a placebo or has replicated the treatment protocol for masking still utilize the term Hawthorne effect instead of placebo effects[11, 17] *(Table 2)*. Even in specialities such as psychology, it is often unclear on what term is more suitable. The Hawthorne effect is either considered as placebo effect under another name or as an acceptable equivalent to placebo effect to fit the expected results of an experiment.[26] The relative confusion in using these terms seem to reflect in clinical studies themselves where it becomes virtually impossible to identify or differentiate between Hawthorne and placebo effects.

Study Design Options to lower the Placebo Effect

In periodontal double-blind clinical trials, the use of a placebo is an accepted part of the study regimen and any significant effect over a placebo is considered as a standard to establish the efficacy of a treatment protocol. However in periodontics, there are a paucity of trials which have effectively filtered out the "placebo responders" *i.e.* subjects in which the clinical evidence is overshadowed by the placebo effect.[12, 27, 28] The impacts of a placebo effect can be evaluated clinically and can improve oral health on its own.[27] There is much controversy about improvement in oral health that may accrue from the placebo effect of an examination and the maintenance ritual.[29] However, the difference however is higher (around 40%) in studies involving bone grafts and new surgical procedures[31]; these are situations where the effects of subject perception are negligible. Factors such as improper sample size, year of study, improper design characteristics, improper recruitment pattern, origin of the patients and expectations of the examiner/examinees can contribute to the presence of placebo effect in a study.[31] In this regard, reducing the placebo effect is imperative primarily to minimize placebo bias in trials and reduce statistical noise caused by variation in individual patient's placebo responsiveness.[6, 3, 31] Conventional approaches to minimizing this statistical noise, such as increasing the sample size, are inefficient and substantially extend the duration and cost of clinical trials.[6, 31] In a conventional RCT, increasing the sample size, reducing the number of investigators and subjective visits and using whole-mouth raters than site-specific raters are some of the measures to reduce the placebo effect.[32]

It is paramount that the experimental and control groups are observed very closely and the inclusion of a control group overcomes the problem of a possible Hawthorne effect; A meta-analysis of the effect of periodontal treatment on glycaemic control of diabetic patients included only trails having a well-specified control group[33] and a recent trial on the efficacy of nonsurgical periodontal therapy on glycaemic control in type II diabetic patients included a tailored control group to mitigate the Hawthorne effect.[34] A trial on the regenerative potential of EMD utilized four treatment groups to eliminate bias because of placebo effects.[35] If

treatment groups are similar in their pre-test scores, and if a treatment protocol is expected to affect all the groups uniformly, investgators can confidently make a claim about the elimination of Hawthorne effect.[36] Reduction in frequent visits,[37] "masking" the study and placebo sites by the introduction of a "sham" negative control site,[5] simplifying the evaluation protocols[38, 39] and generating uniform subjective awareness expectations across all the groups[40] were some of the strategies used by some recent periodontal trials to minimize the placebo effect. With the current clinical protocols, it is virtually impossible to identify ancillary effects such as the Pygmalion, Halo or the John Henry effects.[41]

IMPLICATIONS FOR FUTURE RESEARCH DESIGNS

Trials to identify placebo-responders

As high placebo response rates can confound treatment trials, there are trials which can identify subjects showing robust response to placebos. These trials are a part of "enrichment" strategies[42] which increasing the chance of identifying treatment effects with a smaller sample size while sparing potential harm to subjects who cannot respond and excluding individuals who tend to over-respond to a treatment regimen.[43]

Placebo lead-in trial

A placebo lead-in trial has an interim period at the beginning of a clinical trial where all participants are given placebos.[44] This enables identification of participants showing exaggerated placebo response who are subsequently excluded from the trial *(Figure 2)*. This increases the ability of the trial to statistically distinguish the effects of clinical response from placebo response.[45] An increase in power from larger effect size in placebo non-responders results in this trial. The disadvantage of this protocol is that the longer trial duration might still fail to eliminate placebo responders.[44] Studies which have utilized this trial have significantly shown that placebo lead-in responders had significantly better clinical scores than their counterparts who were not lead-in responders.[45, 46] The authors however could not find studies in periodontics which utilized a single-blind or a double-blind placebo lead-in period.

Sequential parallel comparison design (SPCD)

The SPCD has two specific stages; the first stage compares the drug and placebo, as in a parallel design and generates a pool of placebo non-responders *(Figure 3)*. The second stage, compares the drug and placebo, as in a parallel design, but utilizes only the placebo non-responders.[47] The main advantages of SPCD are as follows: unlike placebo lead-in, a higher number of patients can be included. There is increase in power for any given sample size from potentially larger effect size in placebo non-responders from reuse of patients. More responses are observed compared to parallel design or placebo lead-in.[48] However, longer trial duration for individual subjects compared to the parallel design and placebo lead-in can be a disadvantage.[49]

Two Way Enriched Design (TED)

The basic premise for the TED design is that a drug should be significantly superior to placebo in achieving short-term efficacy or is superior to placebo in placebo non-responders or is superior to placebo in the maintenance of efficacy in those patients who respond to drug therapy.[46] The TED runs in two specific stages. In the first stage, patients are randomized between drug and placebo. In the second stage, placebo non-responders are re-randomized between drug and placebo and drug responders are re-randomized between drug and placebo.[45,46] All first-stage data, and second-stage data from first-stage placebo non-responders and first-stage drug responders, are utilized in the efficacy analysis *(Figure 4)*.

Apart from the above, combinational trials such as a three-stage clinical trial design[50] and a sequential enriched design[51] are now in vogue as a part of study population enrichment.

The role of ethically appropriate placebo use

As Dr. Bradford Hill has stated, "Is it ethical to use a placebo? The answer to this question will depend, I suggest, upon *whether there is already available an orthodox treatment of proved or accepted value*[52]". According to the Declaration of Helsinki on placebo controls, placebo-driven methodologies should only be used in the absence of existing proven therapy.[53] The CIOMS guidelines on placebo controls clearly

state that placebos should be used only when no effective treatment/replacement exists or when use of placebo control entails minor risks to subjects and using other controls do not give reliable results.[54] Placebo controls are uncontroversial when there is no effective treatment for the population being studied or when effective treatment involves unacceptable side effects for most patients. Studies involving additive therapies to existing accepted treatment protocols can also utilize a placebo.[46] On the contrary, withholding a known effective therapy in a placebo group in a disease has serious consequences for personal health is a strict contraindication for using a placebo.[53] Periodontitis has a widely known and accepted treatment protocol; to what extent the use of placebo groups in clinical trials for a condition with an approved treatment is questionable and may represent substandard treatment.

CONCLUSION

There are several ambiguities behind understanding and describing the placebo effect. The terminology used to describe the placebo effect or Hawthorne effect is inconsistent and is a matter of intensive debate. Placebos themselves have undergone a paradigm shift from being viewed as an inert control to agents which can demonstrate powerful therapeutic effect of their own. The biggest grey area for a researcher or an author is the lack of standard guidelines towards using terms such as placebo and Hawthorne effect. Even after recognizing these effects, there is clearly a paucity in tools predicting the degree and effects of these responses. Additionally, improving clinical trial design towards better understanding, characterizing and minimizing of the placebo or the Hawthorne effect is required.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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