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Dentine hypersensitivity: is there both stimulus and placebo responses in clinical trials?

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Abstract: *Aim:* To determine whether application of a periodontal dressing stopped pain arising from dentine hypersensitivity, objectively assessed with evaporative and thermal stimuli and recorded with Visual Analogue Scale scoring (VAS). *Materials and methods:* 22 subjects completed the single-centre, subject-blind, stratified, randomized, split-mouth study, with a minimum of two sensitive teeth, in at least two different quadrants, displaying a response of ≥30 mm with VAS to evaporative stimulus. One tooth in two different quadrants was identified and randomized to test or control groups. A dressing was applied to all the sensitive teeth in the test quadrant, and either side of the chosen sensitive tooth on the control side. The test teeth were then stimulated for hypersensitivity using evaporative stimuli and then using thermal stimuli. *Results:* Analysis showed that dressing application produced significantly greater reduction in pain ($P < 0.0001$) compared with no periodontal dressing. Single application of a dressing to sensitive dentine provided 95% pain relief associated with thermal stimulus and 85% pain relief associated with evaporative stimulus. *Conclusions:* Application of the dressing to sensitive teeth, dramatically reduced the pain of dentine hypersensitivity following tooth stimulation. When assessing subjects' response to pain-evoking stimuli, perception of pain appears to be altered by sensory factors, prompting a heightened pain response.

Key words: clinical trial; dentine hypersensitivity; evaporative stimulus; pain

Introduction

Clinical trials facilitate researchers to evaluate the efficacy of numerous treatment agents for dentine hypersensitivity. As yet

no treatment modality has emerged as an outright leader, despite staunch attempts to design well-controlled clinical trials conforming to Good Clinical Practice (ICH 1996) (1). Confounding the interpretation of these studies, the same agent may produce a significant result in one clinical trial and a negative result in another.

In explanation, it is possible that the clinical efficacy of current products tested are at the lower end of the therapeutic range, perhaps due to a function of the potency of the active agents or problematic targeting of the required site (2). It is certain, however, that confusion derives from the highly subjective nature of participant reporting, making it extremely difficult to evaluate the pain objectively. It has been well documented in dentine hypersensitivity trials that the placebo effect is profound, and can be as high as 40% (2, 3), limiting the available range for the test agent to show significance. Other compounding issues may be the Hawthorne effect, investigator technique, the natural history of the condition with its episodic behaviour, regression to the mode, patient/clinician relationship and the choice and lack of standardization of objective assessments, all of which can offer further insight and explanation for the variable outcomes of these clinical studies.

Current treatment regimens for dentine hypersensitivity work on two basic principles. First, and probably most commonly, alteration of fluid flow in dentinal tubules. Current evidence indicates that individuals with dentine hypersensitivity have dentinal tubules which are patent from the pulp to the oral environment (4, 5). Further, clinical evidence shows that sensitive dentine surfaces have wider and more numerous tubules than non-sensitive dentine (6). In theory, and based on the hydrodynamic theory (7, 8), it therefore follows that if the tubules are occluded anywhere along their length, hydraulic conductance will be reduced. Good theoretical and *in vitro* evidence exists that occlusion of tubules can occur and hence reduce intratubular fluid movement (6, 9) yet there are no unequivocal clinical data that purport that the active agents consistently stop the pain of dentine hypersensitivity by occlusion of tubules. The second theory is modification or blocking of pulpal nerve response with, for example, potassium ions, which may reduce intradental nerve excitability by diffusing along the tubules and raising the concentration of local extracellular potassium ions, hence blocking intradental nerve function (10).

The aim of this study was to determine whether application of a periodontal dressing as a treatment regimen would stop or reduce the pain of dentine hypersensitivity. Application of the periodontal dressing would be in considerable bulk compared with application of sealants and dentine bonding agents. The dressing would completely shield the identified tooth, not just the sensitive area, from external stimuli, with a barrier of at least 5-mm thickness. The nature of the dressing, placed on the identified surface of the tooth, would be a thick and viscous layer, blocking the orifices of tubules. The dressing would also prevent external stimuli causing fluctuation of the dentinal tubular contents due to the consistency and dimensions of the media. Thus, the investigation is a proof of principle scenario, the primary objective was to determine whether application of a periodontal dressing occludes the tubules and stops or reduces the pain derived from evaporative and thermal stimuli due to dentine hypersensitivity. If the theory is true, this treatment option would clinically confirm that shielding the sensitive tooth is a good mechanism of pain control, and supports the occlusion of tubules treatment therapy. The secondary objective was to further understand the clinical methodology for the evaluation of agents that will occlude dentinal tubules in subjects with dentine hypersensitivity.

Materials and methods

The study was a single-centre, subject-blind, stratified, randomized, split-mouth design clinical trial conducted in the Clinical Trials Unit at the Bristol Dental Hospital. The study was conducted in accordance with the guidelines documented in Good Clinical Practice and ethical approval was granted from the Central and South Bristol Research Ethics Committee. Subjects were recruited from the population working at the United Bristol Healthcare Trust and Bristol University just prior to the study. Following written informed consent, medical history, current/concurrent medication, oral soft tissue assessment and examination of inclusion/exclusion criteria, screening for dentine hypersensitivity was performed. Up to 30 healthy male and non-lactating female subjects, who met the entry criteria, aged at least 18 years with dentine hypersensitivity, could be enrolled into the study to ensure at least 20 evaluable subjects completed. No formal sample size calculation was performed but 20 was considered to be logistically feasible and adequate to assess this proof of principle study. Subjects needed a minimum of two sensitive teeth (in different quadrants) showing buccal recession and exposed dentine, and displaying a response of ≥30 mm on a 100-mm Visual Analogue Scale (VAS) to a 1-s evaporative stimuli. The 1-s blast of air was delivered from a triple air dental syringe directed perpendicular to the buccal area of recession, about 1 cm away from the tooth, with 40–65 psi and a temperature of 19°C ± 5°C. All teeth were tested for dentine hypersensitivity

with the evaporative stimuli. The study teeth were to demonstrate no periodontal involvement. Two teeth each in a different quadrant, were identified for further study, these teeth being contralateral in nomenclature, and either first or second premolars or first molars. To ensure levels of sensitivity were balanced across treatment groups, the two identified teeth in different quadrants were assigned, based on severity of pain, to either the test or control treatment group using stratification of the VAS score results for the evaporative stimulus. Using the participants' VAS scores for the identified teeth, these were deemed 'highest' or 'lowest' and then the treatment allocated by subject in ascending order by the study site personnel using a randomized schedule provided by the Biostatistics Department, GlaxoSmithKline Consumer Healthcare, Parsippany, NJ, USA. This ensured half of the subjects were allocated to have the test quadrant on the side with the higher VAS scores (site A) and half on the side with the lower VAS scores (site B). As only the study subject is blinded to designation of test and control quadrants, a strategy for unblinding of study staff was not required. All subjects were asked to refrain from eating, drinking or brushing their teeth 45 min prior to sensitivity evaluations. The VAS is a 100-mm line in length, the extremes of the line representing the limits of pain a patient may experience from the external stimulus, the left end representing no pain and the right end representing the worst pain. The participants are asked to mark across the line to indicate the intensity of the pain after applying stimulus (11).

Following screening and recording baseline evaporative scores, baseline thermal records were taken for the identified teeth in different quadrants prior to periodontal dressing (Coe-Pak®, GC America Inc., Alsip, IL, USA) placement. The thermal stimulus was an application of an ice stick taken from an eppendorf, placed on the buccal recession defect for 1 s, or less if the pain was very severe. The dressing was then applied to cover the buccal surfaces and gingival margins of all the sensitive teeth in the test quadrant and one tooth either side of those with sensitivity. This particular periodontal dressing is eugenol free and is based on petrolatum and denatured alcohol. On the control side, Coe-Pak was placed either side of the sensitive control tooth, to cover all other sensitive teeth. The aim of this 'sham' treatment being to try and blind the subject to the identity of the treatment versus control side. The test teeth were then stimulated for dentine hypersensitivity through the periodontal dressing using evaporative followed after a couple of minutes or until the pain was no longer perceptible, by thermal stimuli with the periodontal dressings still *in situ* over the teeth. The pain was recorded by the subject with VAS. The primary outcome measures were the difference between treatments with respect to reduction in the pain VAS scores from baseline for evaporative (air) sensitivity and thermal (ice) sensitivity.

Periodontal dressings were then removed after the pain assessments were completed. At the end of the study, subjects were given advice regarding treatment for sensitivity. Any adverse events were recorded. Subjects completed the study assessments on one session hence the follow-up was performed at the same visit. The periodontal dressing chosen has been used in periodontal procedures for over 40 years, having an exemplary safety record with very few reported adverse reactions.

Statistical methods

The primary analysis of the effect of the periodontal dressing was based on the difference between treatments with respect to the reduction from baseline in the pain VAS scores. Treatment groups within subjects were compared using SAS PROC MIXED. The analysis used a model that includes fixed effect for treatment and baseline score as a covariate with subject as a random factor.

Results

Twenty-two subjects completed the study consisting of five males and 17 females all of which were Caucasian with a mean age of 39.2 years. Oral soft tissue assessments were only conducted at baseline and therefore there were no findings associated with the test product. No adverse events were reported. No results were missing from the analysis, as the study was performed on one single visit.

Following identification of the sensitive teeth and application of the dressing, the results of the teeth tested with evaporative stimuli showed the mean baseline evaporative VAS scores were 58.68 mm for the test side and 58.27 mm on the control side. The analysis of evaporative pain reduction showed that test side produced significantly greater reduction ($P < 0.0001$) (adjusted mean 49.82 mm) in pain compared with the control side (adjusted mean 23.72 mm). Figure 1 depicts the reduction in VAS score for the evaporative stimulus from baseline.

With regard to the thermal stimuli results, the mean baseline thermal VAS scores were 71.41 mm on the test side and 75.59 mm on the control side. The analysis of thermal pain reduction showed that the test side produced significantly ($P < 0.0001$) greater reduction (adjusted mean 69.34 mm) in pain compared with the control side (adjusted mean

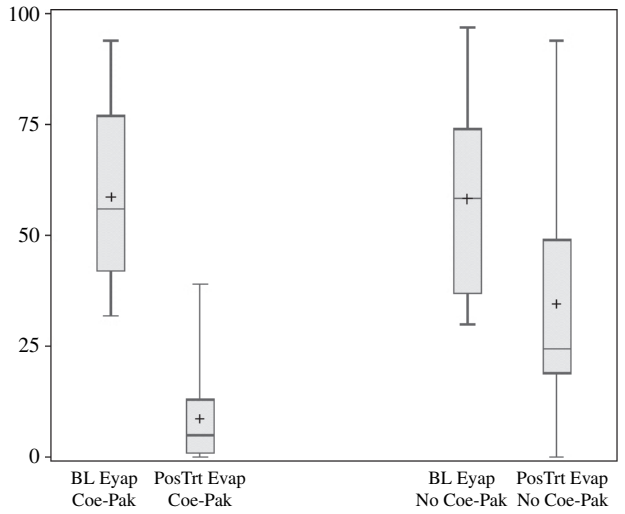

Fig. 1. Reduction in Visual Analogue Scale score for evaporative stimulus from baseline.

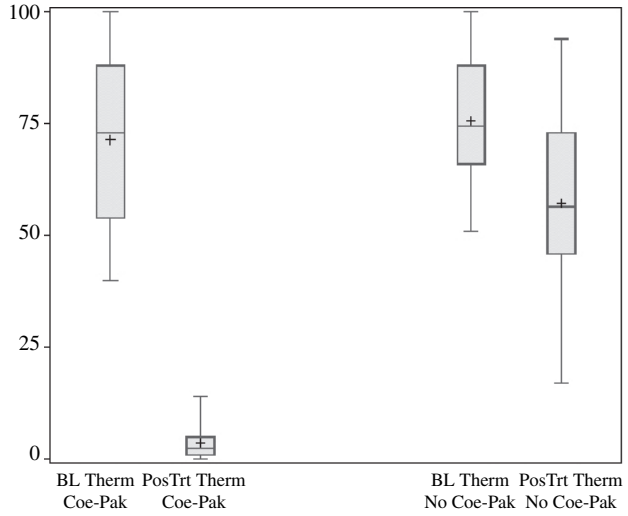

Fig. 2. Reduction in Visual Analogue Scale score for thermal stimulus from baseline.

16.93 mm). Figure 2 depicts the reduction in VAS score for the thermal stimulus from baseline.

Discussion

Pain is considered a multidimensional experience consisting of motivational, cognitive, affective and discriminative components (12). The pain associated with dentine hypersensitivity is mostly acute (sharp and shooting) but can be chronic (dull, throbbing and aching) in nature (13). The clinical measurement of this pain is usually assessed, as in this study, subjectively by the individual's own assessment of the pain severity in response to the presenting stimuli. An alternatively approach has employed the semi-subjective judgement of the subject's pain related behaviour recorded by an observer, e.g. Schiff test (14). Further, the objective assessment of pain-related responses, e.g. measurement of ventilatory function associated with thoracic and abdominal pain can be assessed. Pain is an emotional as well as sensory experience and subject to convergence of nociception, it may not be directly proportional to the severity of the stimulus (15), making assessment fraught with difficulties. As a result, this may lead to the inability to conclude treatment efficacy of a product. This study aimed to overcome these challenges by comprehensive pain reduction with the treatment product.

The outcome of this pain study showed that completely shielding the sensitive tooth resulted in highly significant pain reduction in response to stimuli elicited from evaporative and thermal sources, mostly likely due to both inhibitory contact of the stimuli with the dentine surface and occlusion of the dentinal tubules. The result was expected and confirms the progression and development of treatment regimens which aim to achieve these ends. The efficacy of the treatment modality and comparison to a 'dummy' treatment completely overwhelmed other compounding factors so often detrimental to clinical trials, and proved the principle, using an effective model. An unexpected phenomenon occurred, however, with a minor pain response recorded for both evaporative and thermal stimuli, more pronounced with the former, on the test side. For the reasons stated, this should be impossible.

This finding is most interesting and may relate to the assessment of the pain severity in response to the presenting stimuli. The choice of stimuli was based on a review of previous studies (3, 16–19). The evaporative and thermal stimuli are widely advocated objective assessments for evaluating therapeutic agents in dentine hypersensitivity studies, although limited data are available to establish reproducibility of these pain-evoking stimuli (20). They have been developed to mimic the pain response similar to the natural aetiological agents, e.g. mechanical, evaporative, thermal or osmotic stimuli, with clinical success usually defined by achieving statistical significance ($P < 0.05$) with respect to an agreed clinical outcome. Holland et al. (21) recommended that at least two hydrodynamic stimuli should be used and that a reasonable time lapse should be advocated between stimuli; this is yet to be defined! Further, the sequence of application should be the least severe first, e.g. with tactile before evaporative (22, 23), hence the evaporative stimulus was applied prior to the thermal stimulus at 0°C. Stimuli should be quantifiable, reproducible and clinically relevant (24).

The triple syringe air blast (dehydrating or evaporative stimuli) is the most frequently used stimulus for evaluating dentine

hypersensitivity (25), and is generally considered the most similar to the naturally evoked pain, not tending to cause pain from non-sensitive teeth. The stimulus effects start when evaporation of dentinal fluid occurs, increasing the fluid flow and activating the hydrodynamic process (26). The evaporative stimulus is considered a combination of thermal and evaporative stimuli, the effect depending on the duration and temperature (9, 27), the evaporative component being the dominant stimulus in most clinical studies (9). The generally accepted stimulation is a 1-s blast (9). Elongated air blasts may cause odontoblasts to be aspirated up the tubules.

Thermal stimuli are also frequently used to evaluate dentine hypersensitivity in clinical trials. These stimuli are also very accurate in reproducing the pain experienced in everyday activates. Most hypersensitive teeth will respond to cold stimuli (28, 29). The temperature which appears to elicit a constant and reliable response reviewing publication is 0°C (3, 14, 19). Further, subjects tolerate cold stimuli better than hot and there is less chance of pulpal damage (9).

Hence, the inclusion of these two stimuli, in the order documented in the study protocol are well recognized and frequently utilized. One would feel justified in conjecturing that no pain would be expected on the test side. Yet the outcome of this study revealed a different scenario. The finding that participants gave a response, albeit minor, to the stimuli when the test tooth was completely obscured is somewhat surprising. The hypothesis being that the bulk of periodontal dressing would be sufficient to stop these stimuli evoking pain in teeth known to have a diagnosis of dentine hypersensitivity determined with the evaporative stimulus.

In the study documented in this paper, it is extremely unlikely that the evaporative and thermal stimuli could have been detected by the subjects on the test sites, due to the thickness and consistency of the periodontal dressing. The subjects knew that the two teeth chosen from the screening procedure for further investigation were definitely sensitive, as they were painful initially to the evaporative stimuli. Following identification, randomization and dressing placement, the control teeth scored highly for the thermal and evaporative stimuli, as expected. Unexpectedly, overall the test teeth showed a small pain response to the evaporative stimulus and very small pain response for the thermal stimulus, although these scores were highly significantly less compared with the control sites. All subjects scored greater than zero at the test site for the evaporative stimulus. In explanation, the subject could hear the evaporative stimulus, knew the tooth was sensitive, could anticipate a pain response and gave a pain response greater than zero. The subjects could not tell when the thermal stimulus was applied but still anticipated pain, with a frequent comment of, 'I didn't realise the test had been done', with a few participants scoring greater than zero. Unfortunately, the exact number of these comments was not recorded. It is proposed that the anticipation of pain derived from the evaporative stimulus increased the subjects' perception of severity of pain enhanced with the auditory stimulation, and examining the results, this appeared to be in the region of 15%. The moment of thermal application could not be detected by the subject; however, there was still anticipation that pain would be experienced, and hence a degree of pain, although at a much lower level 5%, was recorded. In reality, it was thought that the subjects would not be able to detect any pain at all from these standardized, controlled conditions. If they did, it would be expected that the thermal stimulus, which overall causes more severe pain than the evaporative stimulus (29, 30), would lead to more pain on the test side than the evaporative stimulus.

In acute pain, the severity of the pain is approximately proportional to the strength of the stimulus but is also related to the psychological state of the subject with anxiety and stress of pain correlating well with the subjects' assessment of pain (15). In particular, an increase in state anxiety, which is the anxiety a subject feels as a result of circumstances or anticipation, correlates well with the subjects' increase symptom reporting of pain (31).

Another phenomenon which may have occurred in this study, as with so many dentine hypersensitivity studies, is the placebo effect (3, 32). It is possible that both test and control groups were affected by this factor, although, in this study, only to a minor degree on the test side due to the overwhelming effect of the active agent. However, just placing a dressing on the control side, avoiding the sensitive tooth was enough to reduce pain from stimulation due to the placebo effect. Further, it is possible that re-stimulating the sensitive tooth gives a different response to the first stimulus for as yet, no evidence is available for pulpal recovery time. These factors could explain why the control side did not show identical degrees of pain on stimulation pre- and post-dressing placement.

The phenomena observed can be partially explained by looking to the mutual contribution of conditioning and expectancy mechanisms (33). Conditioned responses (CRs) are the result of the pairing of a neutral stimulus with a stimulus that elicits an unconditioned response Through association a neutral stimulus becomes a conditioning stimulus (CS). In this study, the pairing of the evaporative stimulus with the auditory stimulus leads to a positive association between the neutral stimulus, sound and a 1-s blast of air to sensitive dentine, the unconditioned response. The lack of any significant neutral sti-

mulus when applying the thermal challenge explains why the recorded pain response was so small.

Similarly, placebo response is mediated by mechanisms involving both conscious and non-cognitive expectancies. The administration of placebo, in this case a 'sham' application of dressing, elicited an expectation for a particular effect. That expectation produced a lower pain response. Integrating this with a conditioned learning mechanism, where the information value of the CS is important, it is reasonable to see how the recipient 'learns' to adjust their response based upon their expectation of pain severity.

These mechanisms support the findings of this study and raise further questions about the reliability of the evaluation parameters we employ in dentine hypersensitivity. The authors feel further research needs to be undertaken on the accuracy and reliability of these test stimuli.

With regard to the other criteria followed in the protocol, the split-mouth study design was chosen for this trial as it is a highly effective, efficient model for professional application of sensitivity products. The subject acts at their own control which is a very powerful tool statistically, and the methodology of choice. This methodology could be used as the treatments applied could not contaminate the opposing side of the mouth and vice versa. Once teeth were identified as demonstrating dentine hypersensitivity, two teeth were highlighted for investigation. These teeth afforded different quadrants to satisfy the split-mouth design for this trial and fortuitously teeth of the same denomination were paired in each subject, which is advantageous with respect to matching the teeth as closely as possible for structure and hence pain response. None of the teeth chosen were heavily restored, used as a bridge abutment or demonstrated cracks in the enamel or dentine which may have given a similar pain response but from a different aetiology. Hence, an ideal matched tooth design and protocol design for this type of study were achieved.

In summary, the hypothesis was proved and this gives strong credence to the hydrodynamic theory of pain and subsequent pain reduction treatment modalities occluding dental tubules. The expectation of a response to a stimulus and an effect of a treatment, however, were both observed in this study. This suggests that in clinical trials the 'stimulus and placebo' effects can confound the outcome of the studies albeit in the counter directional ways. The periodontal dressing, whilst bulky in this study, could be refined into a more discrete dressing which could then be applied to the teeth as and when necessary by the individual as an over-the-counter product.

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