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Mind the gap—What is the appropriate time interval between sequential dentine stimuli to elicit a dentine hypersensitivity pain response in clinical studies?

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ABSTRACT

Objectives: To determine the time interval required for a tooth diagnosed with DH to recover from a stimulus (cold air-blast/tactile) and respond with a similar elicited pain response to a repeat stimulus.
Methods: A single-centre, non-randomised, clinical study in healthy adult volunteers. Eligible participants with ≥1 tooth with either a qualifying Schiff score ≥2 following cold air-blast or tactile Yeaple score of ≤20 g were allocated to tactile or air-blast group. Following primary stimulation, the designated tooth was restimulated 10, 5, 2 min and immediately after initial pain cessation. Pain was recorded with participant VAS and investigator Schiff for air-blast.
Results: 40 participants completed the study per group. There was a significant difference in VAS scores for tactile 4 delay intervals ($p < 0.001$) but not air-blast stimulus, and a significant difference in mean change in VAS score from immediate to two-minute delay between stimuli (8.0 tactile vs 0.8 air-blast, $p = 0.011$). VAS scores in response to either stimulus showed very wide variation between participants, but changes over delay intervals within participants were relatively slight. There was a significant progressive decrease in mean Schiff score with shortening delay intervals from 10 min (2.38) to stimulation immediately after pain cessation (2.15), $p = 0.018$.
Conclusions: The findings suggest healthy teeth recover after DH stimulation more quickly following an air-blast than tactile stimulus, with around 2 min allowing recovery from both. Many factors including habituation and pain measurement subjectivity need to be considered. It would be prudent for future studies to use of ≥3 min delays.
Clinical significance: No clinical study has attempted to determine the appropriate interval between successive stimuli in DH patients. The results will impact directly on the conduct of DH trials. These findings suggest the interval could be reduced to around 2-min, but the current standard of 5-min is sufficiently long to give valid results.

1. Introduction

Recent figures demonstrate that the prevalence of dentine hypersensitivity (DH) oral pain is high globally. A 7 European country study of more than 3500 adults reported 1 in 2 suffered from DH [1], with a similar European study 10 years previously in young adults finding 1 in 3 individuals were affected [2]. Both studies also confirmed the condition significantly negatively affected quality of life metrics. These European prevalence figures are similar to those reported from DH studies in China [3-5].

DH may be defined as a short, sharp arresting pain caused by stimulation of exposed dentine on crown and/or root of a tooth by a naturally occurring stimulus [6]. DH pain ceases rapidly following stimulus withdrawal, is usually associated with multiple teeth, can be episodic as the dentine tubules change from occluded to partially occluded or unoccluded status, and negatively affects quality of life [6]. Importantly,

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for DH pain to occur, dentine must be exposed (lesion localisation) with dentine tubules patent from oral to pulpal surface (lesion initiation) [7,8].

The hydrodynamic pain theory proposed by Brännström [9-11] is the currently accepted pain pathway for DH. Various stimuli, evaporative (cold air), cold thermal (cold drinks/foods), tactile (e.g. pressure from toothbrushing) and osmotic (sugary/sour foods and drinks) evoke fluid shifts in the dentine tubules with subsequent activation of mechanoreceptors of the intradental nerves in the deep dentine and pulp [12-14]. The nature of DH pain, sharp, localised, and lasting only for the duration of the stimulus [15], corresponds to pain associated with A-fibre nociceptor activation [8]. In contrast, pulpal C fibres do not respond to stimuli that evoke DH, but to intense heat, trauma and other noxious stimuli activating thermal receptors, which is not classified as DH and dentine does not need to be exposed for a pain response [8,16,17].

Common pitfalls in the differential diagnosis of DH include conditions that give rise to pulpitis, which is characterised by an inflamed hyper-responsive pulp injury [18] or infection [19,20], eg vital tooth bleaching, caries, cracked tooth, active periodontitis, ginding and clenching, failing restorations to name but a few. The similarity between DH pain and the pain initiated by other oral conditions, together with the fact that oral features suggestive of DH are also common to other oral disease and conditions, make the diagnosis and treatment of DH challenging for the oral healthcare professional.

Evaporative, cold thermal, and tactile are the stimuli currently advocated in DH clinical studies [21] as these replicate natural DH stimuli, unlike for example electrical stimuli. Electrical stimuli are not physiological [22] and can be reused quickly unlike osmotic stimuli, which needs lengthy time intervals between applications to remove residual osmotically active substance [23]. Evaluation of treatment modalities to alleviate the pain of DH conventionally follow a randomised controlled double blind study design using these physiological and controllable stimuli [24]. The guidelines for the conduct of DH studies recommend that two of these three (Evaporative, cold thermal or tactile) stimuli should be applied at screening and baseline to confirm the diagnosis of DH in a specific tooth and at subsequent time points in a treatment efficacy study, [24,22]. The decision by Holland et al. [24] to use two stimuli for DH studies was made by unanimous decision in the guideline consensus meeting as an effort to increase diagnostic sensitivity due to the potentially subjective and variable nature of testing for DH [24]. In the Holland et al. consensus paper [24] it states that dentine sensitivity may be different for different stimuli [22,25] and it is recommended that least 2 hydrodynamic stimuli should be used. The least severe stimulus should be applied first [26]. The interval between stimulus applications should be specified in the protocol and be of sufficient duration to minimize interactions between stimuli. The appropriate interval is, as yet, unknown, and is likely to vary for different types of stimul. Newcombe et al. [27] provide a summary of DH trial design and analysis [27]. Pain is the principal and primary outcome recorded from the standard DH stimuli, either from the participant's perspective (yes/no), Visual Analogue Scale (VAS), verbal descriptors or clinician's perspective e.g. Schiff score [28]. Assessment of pain is inherently subjective, and perception is not always directly proportional to the extent of damage produced by a defined stimulus [29].

Research with animal models suggests that following stimulation of DH there is no acute or chronic pulpal inflammation present [30-32]. In support of these findings, animal models show that reproducible intradental nerve responses to probing of dentine can be recorded when there are only a few seconds between each mechanical stimulus application [33,34]. For clinical studies Holland et al. [24] states that "The interval between stimulus applications should be of sufficient duration to minimize interactions between stimuli. The appropriate interval is, as yet, unknown, and is likely to vary for different types of stimuli." In theory, if the pulp is heathy at the time of testing a second stimulus could be applied immediately upon cessation of DH pain from the first. As there is no research to confirm the appropriate time interval for repeatability of the pain response, the time needed for pulpal recovery is estimated, with a gap of 5 min between stimulating the same tooth with sequential stimuli commonly used [35,36]. This can result in volunteers in a clinical study spending a considerable time in the dental chair, while multiple teeth are stimulated which may be stressful and wasteful of resources.

The aim of this study was to investigate the time interval needed for a tooth diagnosed with DH to recover from a first stimulus (cold air-blast or tactile) and respond with the same or similar elicited pain response to a repeat application of the same stimulus. The pain response between consecutive stimuli was compared, the study hypothesis being that with a healthy pulp no material difference in pain scores would be detected following repeated stimulation even at the shortest time lag. The outcome of this study will help to inform clinical trial design for DH sufferers and minimise visit time for study volunteers enrolled in DH studies.

2. Materials and methods

2.1. Study design

This was a single-centre, non-randomised, clinical study conducted by a UK Dental clinical trials team and conducted in accordance with Good Clinical Practice. The study was granted ethical approval by a University Research Committee. Two groups of adults with at least one sensitive tooth were recruited, the aim being to recruit one group had a tooth identified that responded to the cold air stimulus, and a second group had a tooth identified that responded to the tactile stimulus.

2.2. Participant recruitment

Participants were recruited from the study site database of individuals who had expressed an interest in taking part in dental clinical trials. Potential participants were sent a study information sheet and invited to a screening appointment. Eligible participants were healthy adults aged $\geq$18 years, in good oral and general health and a self-reported history of DH lasting >6 months and <10 years, with one or more non-wisdom tooth subsequently clinically confirmed as having DH as evidenced by qualifying levels of tactile (Yeaple probe 20 g) [37] or evaporative sensitivity (air-blast Schiff score $\geq$2) [28]. Only teeth which exhibited exposed dentine in the cervical area, modified gingival index score [38] of 0 adjacent to the test site and no mobility or other pathology were selected as study teeth. Exclusion criteria included current participation in other clinical studies, untreated caries or periodontal disease, current orthodontic treatment, taking medications deemed to affect pain response, dentine exposure with deep, defective, or facial restorations, use of crown, veneer or bridge abutment, or any other condition that in the investigator's opinion would affect study validity.

2.3. Study procedures

Participants who gave informed consent were assessed for eligibility. The trained study dentist who was calibrated with a gold standard examiner (weighted kappa 0.870) undertook a medical history, as well as oral hard and soft tissue examination. Participants meeting all specified eligibility criteria were enrolled in the study. Enrolled participants were allocated to the air-blast or tactile group as dictated by their DH, recruitment continuing until there were 40 in each group. A test tooth that met study criteria was selected and interrogated with the assigned stimulus. If the DH threshold was met (confirmation of subject DH pain and cold air blast Schiff sensitivity score $\geq$2; or tactile stimulus with a Yeaple probe tactile threshold 20 g eliciting DH pain), the pain score was recorded as the baseline DH positive result and the participant was eligible for further testing.

In each group the selected tooth was restimulated with the same stimulus with decreasing time intervals between each stimulus: 10 min after baseline, 5 min after last stimulus, 2 min after last stimulus and immediately after the volunteer indicated the pain had stopped from the previous stimulus. After each application of the stimulus, the pain experienced by the participant was recorded using the same measures as at baseline. Participants were able to withdraw from the study at any time.

2.4. Measures of DH

2.4.1. Evaporative air stimulus

The evaporative air stimulus was applied by directing a one second application of air from a standard dental syringe at 60 psi (± 5 psi) with operating temperature in the range 19 °C (±5 °C), held perpendicular to the tooth, at a distance of approximately 1 cm from the exposed dentine surface. DH pain was scored by examiner Schiff [28] as follows: 0, Subject does not respond to air stimulation; 1, Subject responds to air stimulus but does not request discontinuation of stimulus; 2, Subject responds to air stimulus and requests discontinuation or moves away from stimulus; 3, Subject responds to stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus. Participants were also asked to record their DH pain using a VAS 100 mm line from "no pain" to "worst tooth pain".

2.4.2. Tactile stimulus

The tactile stimulus was applied by using a constant pressure probe using a calibrated Model 200A Yeaple [37] electronic pressure sensitive probe (Yeaple Research, Pittsford, NY, USA). Exposed cervical dentine was stroked perpendicular to the exposed dentine at a pre-set force 20 g. If there was no indication of discomfort the tooth was considered to be non-sensitive. Once the baseline level of stimulation was established, the same pressure was reapplied at each subsequent stimulation.

A trained member of the study staff calibrated the Yeaple probe before use on each day participants were assessed.

Participants were also asked to record their DH pain using a VAS 100 mm line from "no pain" to "worst tooth pain".

2.5. Statistical methods

For the power calculation for the change in Schiff score, a conservative approach assumes a zero correlation leading to an unpaired *t*-test. Previous data within the study group indicated that 20 % of teeth scoring 2 or 3 score 3. Correspondingly, using 40 participants allows detection of a change from the resulting baseline mean of 2.2 to either 2.5 (50 % at 2, 50 % at 3) or 1.875 (25 % at 1, 62.5 % at 2 & 12.5 % at 3) with power 80 %.

Trends in VAS scores across the 4 stimulations were examined graphically, both aggregated across participants and showed tracks for individual participants. Changes in score within stimulus groups were examined by paired *t*-tests and 2-way analysis of variance. The Spearman rank correlation was used to examine the relationship between Schiff scores and corresponding VAS scores, and also between changes in these scores between stimuli.

3. Results

Eighty participants were recruited between the 9 November 2023 and 4 December 2023. The 40 participants in the tactile group had mean age 43.4, 72.5 % were female. The 40 participants in the cold air group had mean age 43.7, 80 % were females. Participants were almost exclusively White (85 % cold air/ 90 % tactile), demographics being comparable across both groups. All recruited participants completed the entire study. No adverse effects were reported.

3.1. VAS

Fig. 1 summarises the mean VAS scores when the stimuli were repeated after 10, 5 and 2 min and immediately with mean scores presented in Table 1. Mean scores were rather higher (worse) for cold air than for tactile stimulation.

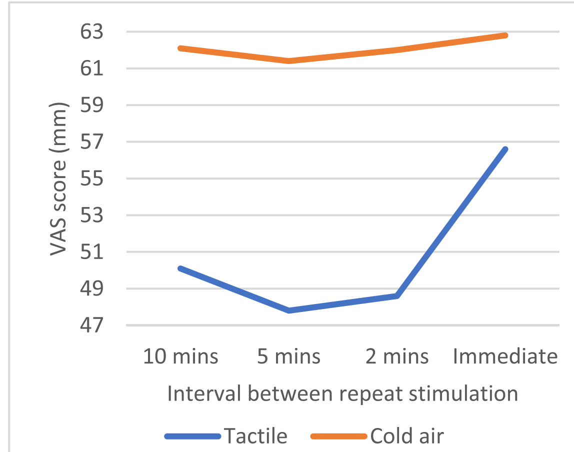

Fig. 1. Participant VAS score by delay and stimulus.

Comparing the results for all four delay intervals by two-way analysis of variance, for the cold air-blast stimulus differences in VAS scores did not approach statistical significance ($p = 0.90$). In contrast, there was a highly significant difference between the 4 delay intervals for tactile stimulation ($p < 0.001$).

Comparing sequential stimuli, changes in VAS score from 10 to 5 min and from 5 to 2 min were not statistically significant for either stimulus. However, for tactile only, immediate re-stimulation was significantly worse than stimulation after two minutes, mean difference 8.0 (95 % CI 4.1, 11.9; $p < 0.001$), and the between group mean difference for this interval was also statistically significant (mean difference 7.19; 95 % CI 1.71, 12.67; $p = 0.011$).

However, underlying the above summary analyses, Fig. 2(A and B) show the trends within air and tactile groups respectively, tracking individual participants. Most participants tended to have fairly consistent responses, so those who started with high DH scores retained high DH scores and vice versa for each stimulus, but there was gross variation within each stimulus group.

3.2. Clinical scores, and their relationship to VAS scores

For the cold air group, the frequency distributions of the Schiff scores for the 5 stimulations are outlined in Table 2.

There was a progressive decrease in mean Schiff score from 2.38 at baseline to 2.15 for immediate re-stimulation, a decrease that though small, was statistically significant (mean difference −0.225; 95 % CI −0.409, −0.041; $t = -2.467$; $p = 0.018$). Analysis that was supported by two-way analysis of variance of the mean differences in Schiff score between the 5 stimulations ($p < 0.005$).

For the cold air group, the Spearman rank correlations between Schiff and VAS at each simulation were moderate and statistically significant, however, the correlations between changes in VAS and changes in Schiff from one stimulation to the next were weaker and non-significant (Table 3).

In the tactile group, the participants were tested each time with the

Table 1
Summary statistics for Cold Air VAS and Tactile VAS.

VAS score mean (SD)	Time interval between stimuli			
	10 min	5 min	2 min	immediate
Cold air	62.1 (19.3)	61.4 (21.1)	62.0 (21.7)	62.8 (24.6)
Tactile	50.1 (19.3)	47.8 (23.3)	48.6 (24.0)	56.6 (25.3)

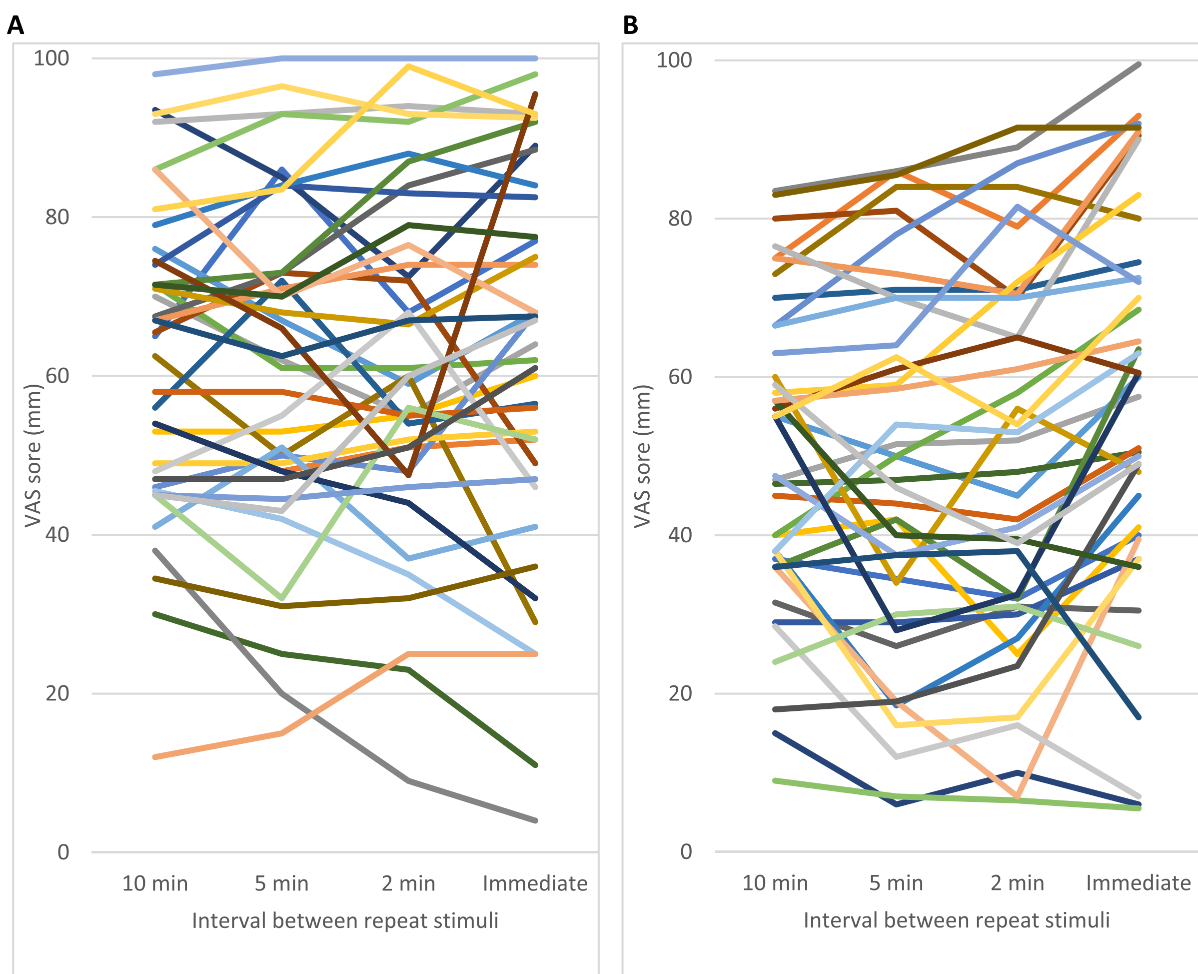

Fig. 2. Participant VAS scores after stimulation with A: cold air-blast, B: tactile. Each line represents a different participant.

Table 2
Frequency distribution and mean for Schiff score by delay before re-stimulation.

Time point	Schiff score frequency (%)			Mean Schiff score
	1	2	3	
Baseline	0	25 (62.5 %)	15 (37.5 %)	2.38
10 min	0	25 (62.5 %)	15 (37.5 %)	2.38
5 min	2 (5.0 %)	23 (57.5 %)	15 (37.5 %)	2.33
2 min	5 (12.5 %)	20 (50.0 %)	15 (37.5 %)	2.25
Immediate	8 (20.0 %)	18 (45.0 %)	14 (35.0 %)	2.15

Table 3
Spearman rank correlation between Schiff and VAS at each stimulation with a cold air-blast, and the correlation between changes in Schiff and VAS from one stimulation to the next.

		Rank correlation between Schiff and VAS	*p*-value
Stimulus time point	10-min	0.45	0.004
	5-min	0.42	0.007
	2-min	0.39	0.014
	Immediate	0.55	<0.001
From stimulus to stimulus	10-min to 5-min	−0.06	0.73
	5-min to 2-min	0.03	0.85
	2-min to immediate	0.21	0.19

same pressure 20 g that initially resulted in a pain response. Therefore, no analysis corresponding to the above was possible.

3.3. *Time taken to allow re-stimulation*

Table 4 shows summary statistics for the time taken to allow re-stimulation for the two stimulus groups. Five (12.5 %) participants in the tactile group and two (5 %) in the cold air group took longer than 120 s (two minutes) to allow re-stimulation.

4. Discussion

The current guidelines for dentine hypersensitivity studies recommend that at least two hydrodynamic stimuli should be used [24]. However, this rule is not followed dogmatically in research studies and a recent systematic review found that 32 % of papers screened at full text used only one stimuli [6]. The least severe stimulus should be applied first, Gillam and Newman [26] tactile before cold air-blast, and the interval between stimulus applications should be specified in the protocol and be of sufficient duration to minimize interactions between stimuli. The appropriate interval is, as yet, unknown and is likely to vary for

Table 4
Time (seconds) taken to allow re-stimulation

	Mean	Std. Deviation
Cold air group	48	32
Tactile group	56	40

different types of stimuli. The aim of this study was to investigate the time interval that is needed for a tooth diagnosed with DH to recover from the first stimulus (cold air-blast or tactile) and respond with the same or similar elicited pain response to a repeat application of the stimulus.

The study hypothesis that there would be no material difference in pain scores, even at the shortest time interval, due to the pulp being healthy, was supported for the cold air-blast stimulus but not for the tactile stimulus. The findings for the tactile stimulus suggest a healthy tooth recovers around 2 min after DH stimulation and that for DH stimulus reproducibility, there is little difference between 2 and 5 min delay intervals. The results for the cold air-blast stimulus suggest restimulation after either 2 min or immediately after pain cessation will provide reproduceable results, however there is a progressive decrease in Schiff score from stimulation at 10 min or 5 min (Schiff scores always identical at these time intervals), to stimulation immediately after pain cessation. This trend in the Schiff group may demonstrate habituation to the stimulus.

In the tactile group only, immediate re-stimulation was significantly worse than stimulation after two minutes. This result was surprising given that animal studies have suggested the pulp in DH teeth is healthy [30], and none of the participants in the study had evidence of periodontitis or other condition which could potentially result in pulpal inflammation [39]. It is not possible to explain the increased VAS in the tactile group with immediate re-stimulation, however it could theoretically represent the effect of anticipation [40], potentiation due to carry over effect, or temporary sensitisation of the nerves or central nervous system. The quick recovery makes pulpal inflammation seem unlikely.

Individual participants were quite consistent in their VAS pain responses across each timepoint, however, there was gross variation in VAS pain scores within each group despite all participants being exposed to the same stimuli. In a recent DH trial [41], progression in VAS scores across visits in the two groups showed a very similar pattern to that seen in the present study. Perhaps the relatively good intra-participant consistency but large overall variation demonstrates different interpretations of 'worst tooth pain' or 'no tooth pain' and may take into account previous pain experiences. Imprecision has also been noted for air-blast VAS scores in a recent systematic review, which may be problematic for researchers considering its use as a primary outcome in DH trials [6]. Previous research has indicated that pain perception is subjective [29].

VAS scores were significantly higher for cold air-blast than tactile stimuli at every timepoint except immediate re-stimulation. However, the more pronounced response to cold air likely indicates that in this study the 'pain doses' of cold air and tactile stimulation used were not equivalent. For this reason, the within group comparisons are the more meaningful. For the cold air group, there were moderate correlations between VAS and Schiff scores at each time point that were statistically significant. Yet, changes from one stimulation to the next were not significantly correlated and possibly indicate lower sensitivity of the Schiff score, which is a four-point scale.

VAS scales tend to be less influenced by bias that can be introduced from more precise scale descriptors [21], however, VAS and descriptor scales are not highly and directly correlated with patient perceived pain. While these scales have proven useful in the measurement of high-intensity pain conditions such as post-operative pain [42,43], the nature of low-level pain may not be fully captured by these patient-reported measures, and in clinical studies, discrimination between DH product efficacy may be mediocre [27].

Patients self-report discomfort arising from a variety of stimuli, but the highly subjective nature of DH makes it extremely difficult to evaluate objectively unless the challenge is standardised, controlled and repeatable. Choosing the most appropriate objective, quantifiable and clinically relevant stimuli to initiate the condition of DH on teeth in clinical studies and being able to record subsequent therapeutic pain changes in a treatment efficacy study is key to success. Cold air-blast and tactile stimuli are predominantly the stimuli of choice for DH clinical studies [2] both replicating physiological stimuli and being objective assessments. Whilst both can stimulate DH pain the method of dentine fluid movement is different. Pressing the dentine with a sharp explorer induces sufficient inward fluid shift to exceed the pain threshold. When the pressure is removed, an outward fluid shift occurs due to the elastic recoil of the dentine surface that also activates the intradental nerves [44]. Often only a very small area on the exposed dentine is sensitive to probing [45] and whilst pain can be excruciating for the individual it is not usually as feared by the sufferer as the cold air blast. This could be an explanation for the apparent stronger habituation in the cold air blast group than tactile.

The air blast gives a very effective provocation of tooth sensitivity pain that acts by inducing rapid outward fluid shifts [46]. Cold air blasts evaporate the fluid from the dentine tubules. This in turn produces a cooling of the dentine and an outward fluid shift caused by capillary action. Evaporative fluid movement may occur though small or partially occluded tubules and this makes it a very effective stimulus due to the extensive branching of the tubules near the dentine-enamel junction and subsequent rapid fluid shift movements evoking pain [46]. A wider area of dentine is also stimulated with an air blast compared to the tactile stimulus.

The study authors acknowledge limitations that should be considered when interpreting the results of this study. Firstly, participants recruited to each group were not tested with the contrary stimuli, it therefore cannot be assumed that the stimuli were equivalent. In future, a cross over or split-mouth trial may help to address this issue and also make VAS scores more comparable between groups. In addition, the intervals were shortened incrementally and there is an assumption that the time interval between two stimuli is not affected by any previous stimuli given e.g. there is no carry over effect leading to habituation or anticipatory crescendo. When interpreting the results it should be borne in mind that habituation may well occur, and pain measurement is unavoidably subjective.

The primary aim of this study was to determine the most appropriate time interval for a second stimulation with the same stimulus. Analysis of the 4 delay intervals for cold air VAS were not statistically significant, meaning that it might be possible to undertake re-stimulation in this group as soon as the patient indicates that the initial DH pain has resolved. However, the apparent gradual habituation in this group may need consideration but does not contraindicate immediate re-stimulation. Conversely, in the tactile group the immediate VAS score was significantly higher than all other time points. It might be considered from these results that immediate for cold air and two-minutes for tactile are appropriate re-stimulation intervals for future DH trials. However, 12.5 % of participants in the tactile group and 5 % in the cold air group took longer than 120 s to indicate the initial DH pain had subsided. Therefore, it may be prudent to continue to delay re-stimulation with either stimulus in future DH trials to ensure that all responses are valid. On this basis, 3 min would seem a reasonable delay but there would be no conceivable problems with continuing with the traditional 5-min.

5. Conclusion

The findings suggest a healthy tooth recovers after DH stimulation from cold air blast or tactile pressure around 2 min. However, to be sure of valid results it would be safer to wait until 3 min have passed before re-stimulation and other than being less efficient, there would be no reason to have concerns over continuation of the 5-min interval. Therefore, it would be prudent for future studies to use of delay of $\geq$3 min. Global consensus guidelines with a refreshed standardised protocol need to be developed to best evaluate DH and treatment outcomes to alleviate the pain for the many individuals who suffer this common pain condition. It is the authors' opinion that it will be important for any future guidelines to robustly address the following question, do we really need to use two stimuli in these studies or will one suffice?

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CRediT authorship contribution statement

Alexander Pollard: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Matthew Wright:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Natasha West:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Robert Newcombe:** Writing – review & editing, Formal analysis. **Maria Davies:** Writing – review & editing, Formal analysis, Conceptualization. **Nicola X. West:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Data availability

The data that support the findings of this study will be stored in the publicly available University of Bristol Research Data Repository once the data has been published. Data will be made available to researchers subject to the agreement of the University of Bristol Data Access Committee.

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