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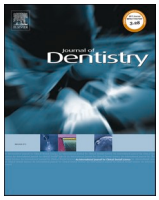

An exploratory randomised controlled clinical trial to evaluate the efficacy of an experimental toothpaste in the relief of dentine hypersensitivity

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ABSTRACT

Objectives: Investigate efficacy of an experimental 3 % polyvinyl methyl ether/maleic anhydride co-polymer (PVM/MA)+5 % potassium nitrate (KNO_3) toothpaste (Test), to reduce dentine hypersensitivity (DH), compared to toothpastes containing: 3 % PVM/MA (Comparator-1) or 5 % KNO_3 (Comparator-2) or fluoride (Negative control), following twice-daily use over 8 weeks.

Methods: A single-centre, 8-week, randomised, controlled, examiner-blind, parallel design, stratified study in healthy participants with ≥2 sensitive teeth. Evaporative air and Yeaple tactile stimuli were measured by Schiff sensitivity score and tactile force. Participants completed a DH experience questionnaire (DHEQ-15) and self-perceived pain numeric rating scale (NRS). Participants were stratified by maximum test teeth baseline Schiff score and randomised to one of four treatments. Mean change from baseline in test teeth for Schiff and tactile force, at 3 days and 2, 4 and 8 weeks, were analysed using analysis of covariance.

Results: 118 participants completed the study. By week 2 the Test paste reduced DH significantly more from baseline compared to Comparator-1, -2 and Negative control for Schiff sensitivity (-0.3 $p = 0.009$, -0.67 $p < 0.001$; -1.44 $p < 0.001$) and tactile force (8.97 $p < 0.001$; 17.71 $p < 0.001$; 32.81 $p < 0.001$) respectively. DH continued to decrease for Test and Comparator-1 to week 8. Significant between group differences were not seen for NRS or DHEQ, baseline imbalances confounding analysis.

Conclusion: The Test toothpaste containing 3 % PVM/MA + 5 % KNO_3 was superior to the other 3 toothpaste treatments in reducing DH at all time points for both DH stimuli over an 8 week period apart from Comparator 1 at Day 3 for the evaporative stimulus.

1. Introduction

Dentine hypersensitivity (DH) is defined as a commonly occurring, recurring short, sharp, arresting oral pain condition in healthy vital teeth resulting from exposed dentine stimulation, resolving immediately upon stimulus removal, and negatively affecting quality of life [1–3]. Data from a 2019 systematic review [2] showed that prevalence ranges from 1.3 to 92.1 %, heterogeneity in part a result of study characteristics such as cohort studied or study setting. In a recent European study prevalence in adults was shown to peak in the 38–47 age group [4].

DH arises following lesion localisation and lesion initiation with a prerequisite of dentine tubules patent to the pulp [5]. Lesion localisation is most common as a result of either gingival recession due to soft tissue loss exposing root dentine or erosive tooth wear resulting in enamel hard tissue loss, exposing coronal dentine [1]. The lesion most often occurs at the cementoenamel junction where the enamel thins to meet the cementum, the buccal cervical region being more vulnerable to both recession and tooth wear compared to the lingual corresponding area [4]. Lesion initiation is primarily caused by erosive tooth wear. With increased life expectancy, and individuals retaining their vital teeth with complete functionality for longer (due to caries and periodontal disease prevention and treatment) and as diets change (with an increased

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consumption of acidic foods and beverage), it is reasonable to expect a higher incidence of DH [1,4,6]. Further, evidence suggests that much early erosive tooth wear commences prior to 18 years of age [4] with prevalence increasing dramatically compared to data 10 years ago [1,4].

Currently, there are two main approaches to managing DH. The first involves products containing desensitising agents such as potassium nitrate (KNO_3). Potassium ions are thought to penetrate exposed dentinal tubules and depolarise the intra-dental nerves, increasing the action potential firing threshold, which reduces the pain associated with DH [7–19]. Many long-term studies (4–12 weeks) have demonstrated the effectiveness of KNO_3 in reducing the pain of DH [10–12]. However, short-term therapeutic effects are not consistently supported by many studies [13,14].

The second approach to managing DH is that of dentine tubule occlusion or surface coverage, this often produces immediate or short -term therapeutic effects with long lasting action if products are used twice daily on a regular basis [3,9]. These include occluding agents such as strontium/stannous salts, bioglasses, arginine/calcium carbonate, which work by sealing or narrowing the dentinal tubules [9]. Stannous fluoride has been identified as one of the most effective occluding agents, owing to its ability to form a protective layer on dentine surface that resists acid challenges, and its ability to occlude dentinal tubules and offer long-lasting protection [16,17]. Bioglasses have the ability to not only occlude dentinal tubules but also help with the regeneration of hydroxycarbonate apatite, which mimics natural tooth mineral however due to their mode of action, dentine tubule occlusion takes a few days to occur [18]. Arginine/calcium carbonate containing formulations form a calcium-rich layer that occludes dentinal tubules with evidence supporting DH reduction when used twice-daily [3].

Co-polymers such as polyvinyl methyl ether/maleic anhydride copolymer (PVM/MA), are commonly included in oral health care products such as toothpastes to facilitate the retention of active ingredients such as fluoride on the tooth surface [19], and have also been shown to occlude exposed dentinal tubules and reduce DH pain symptoms [20–24]. A 12-week clinical study demonstrated the ability of a toothpaste containing PVM/MA to reduce DH compared to a placebo [20]. Additionally [21], showed that PVM/MA toothpaste outperformed a stannous fluoride toothpaste in reducing DH. More recently, the addition of an octadecene/maleic anhydride copolymer to a KNO_3 toothpaste was shown to reduce DH in response to an evaporative stimulus more than a toothpaste containing KNO_3 alone, although the difference did not reach significance [23].

Despite the promising findings from these studies, to date, there are no clinical studies that have evaluated the combined effects of PVM/MA and KNO_3 in comparison to their use alone. It is hypothesised that combining agents with different modes of action (PVM/MA: reported to provide pain relief by dentine tubule occlusion; KNO_3: reported to provide pain relief by nerve desensitisation), could deliver enhanced and long lasting pain alleviation for DH. This proof-of-principle study aimed to assess the efficacy of a toothpaste containing 3 % PVM/MA and 5 % KNO_3 in reducing the symptoms of DH over an 8-week period, with twice-daily tooth brushing. The primary objective of this study was to compare the combined effects of PVM/MA and KNO_3 toothpaste to formulations containing 3 % PVM/MA only, 5 % KNO_3 only, and a regular fluoride Negative control toothpaste with no known anti-sensitivity properties.The null hypothesis was that there would be no difference in the efficacy any of the toothpastes for the relief of the pain of DH.

2. Materials and methods

2.1. Overview of study design and conduct

This was an 8-week, single-centre, randomised, controlled, single examiner-blind study in healthy participants with DH. Participants brushed twice daily with one of four toothpastes: an experimental toothpaste (test) containing 3 % PVM/MA + 5 % KNO_3, a PVM/MA-only toothpaste (Comparator 1), a KNO_3-only toothpaste (Comparator 2), or a regular fluoride toothpaste (Negative control), and DH was assessed after 3 days, 2, 4 and 8 weeks. Participants also self-reported impacts of DH and intensity of pain at all study visits. The primary outcome measures were the change in Schiff score at 4 and 8 weeks, secondary outcome measures were change in Schiff score at the remaining time points change in Yeaple force at all time points and patient reported changes in DH. Conducted at a UK dental school, the study adhered to GCP and the Declaration of Helsinki. Ethical approval was obtained from NHS Research Ethics committee Wales REC 2 (Ref. [22]/WA/0008), and the study was registered at clinicaltrials.org; NCT05243745.

2.2. Recruitment

Potential participants were recruited from the Dental Clinical Trials Unit database of individuals who had expressed an interest in taking part in clinical trials and from local advertisement. Potential participants were provided with a participant information sheet, it was explained that use of a desensitising product within 8 weeks of the study start was an exclusion criteria, and those who were not currently and had not recently used DH products were invited to a screening appointment.

2.2.1. Visit 1 screening

Participants who gave informed consent were first asked about the oral health care products that they were currently using by study staff to ensure they were not using something containing an active ingredient known to reduce DH pain. Participants were then given an oral hard and soft tissue examination and assessed against the study inclusion/exclusion criteria. Gingival inflammation was assessed using the modified gingival index (MGI) [25], range 0 (healthy gums) to 4 (severe inflammation) and clinical mobility was assessed using the modified Miller Index [26], range 0 (< 0.2 mm mobility of the crown in a horizontal direction) to 3 (mobility of the crown > 1 mm in a horizontal direction with mobility in a vertical direction). Two independent, stimulus-based measures of tooth sensitivity (tactile and evaporative) were employed. The tactile stimulus was administered using the constant pressure Yeaple Probe, calibrated daily, whereby force is exerted on exposed dentine starting at 10 g then increased in 10 g increments until participants indicate discomfort [27], this force being recorded as that eliciting sensitivity. DH is indicated if discomfort is felt at 20 g or less. Evaporative (air) stimulus was administered using a dental air syringe, with participant response evaluated using the examiner determined Schiff index (0 =Subject does not respond to stimulus; 1 =Subject responds to stimulus but does not request discontinuation of stimulus; 2 = Subject responds to stimulus and requests discontinuation or moves from stimulus; 3=Subject responds to stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus) [20]. A Schiff score of 2 or 3 indicated DH. A minimum 5-min interval separated tactile and evaporative assessments to allow for tooth recovery.

Eligible participants were adults aged 18 to 65 (inclusive), in good general health with a minimum of 20 natural teeth who self-reported DH that had started at least 6 months earlier. In addition, they had a minimum of 2 non-adjacent teeth with exposed dentine due to facial/cervical erosion, abrasion or gingival recession (as determined by visual and tactile clinical observation), which also had a modified gingival index [25] score of 0 adjacent to the exposed dentine, a clinical mobility [26] score of 0, tactile sensitivity of ≤ 20 g [27] and an evaporative (air) Schiff sensitivity score ≥ 2 [20]. These teeth were identified as eligible for study assessments at Baseline.

Participants were excluded if they had used a DH oral care product or had tooth bleaching within 8 weeks of the screening visit, if they had taken antibiotics within 2 weeks the screening visit, if they had scaling or root planing within 3 months the screening visit, or treatment for periodontal disease within 12 months the screening visit. Participants were also excluded if they were taking daily doses of medication such as

antihistamines that could interfere with their perception of tooth sensitivity, had a tongue or lip piercing, orthodontic braces/bands or a fixed orthodontic retainer, were pregnant or breastfeeding or had a known or suspected intolerance to study products.

Participants satisfying screening inclusion and exclusion criteria were assigned a study number allocated in ascending order as individuals were enrolled. Enrolled participants were provided with a manual toothbrush (flat trim, medium), an over-wrapped non-DH regular fluoride toothpaste (1450 ppm fluoride as sodium fluoride (NaF)), a diary to record their twice-daily tooth brushing and a timer to use during an acclimatisation period of 2 to 4 weeks. Before leaving the clinic participants brushed their teeth once under the supervision of a member of the study team who instructed them to cover the toothbrush head fully with the toothpaste and brush for one timed minute and then record this in their diary.

Between the screening and baseline visits participants were instructed to brush twice-daily for 1 min using the acclimatisation toothpaste in the same way as they had during the supervised brushing, to use only the oral care products provided for the study and to record brushing in their daily diary. Before the baseline and all subsequent appointments participants refrained from all oral hygiene procedures for at least 8 h and refrained from eating or drinking (apart from sips of room-temperature water) for at least 4 h.

2.2.2. Visit 2 baseline (Day 0)

At Baseline, prior to clinical assessments participants completed the validated short form of the Dentine Hypersensitivity Experience Questionnaire-15 (DHEQ-15) [28,29] and rated their self-perceived discomfort using the Numerical Rating Scale, (NRS) [30,31]. DHEQ Section 1 comprises six questions to determine the characteristics of an individual's DH (eg type of pain, causes, frequency) and three questions to rate on a scale of 1 to 10: DH intensity, to what degree it is bothersome, to what degree it can be tolerated. DHEQ Section 2 investigates the impact of DH on daily life and comprises 15 statements across 5 domains (restrictions of daily activities, positive coping mechanisms, avoidance coping mechanisms, social impact and emotional impact) that are rated on a 7 point scale (strongly agree to strongly disagree). The NRS is a self-perceived sensitivity discomfort assessment where participants rate their DH from 0 (no discomfort) to 10 (worst discomfort) by circling the number most relevant. The participant's completed diary of twice-daily tooth brushing was reviewed for study compliance.

The clinical examiner then conducted an oral soft tissue examination and re-assessed DH in those teeth that were identified as eligible at screening using both tactile and evaporative (air) stimuli. A minimum 5-min interval separated tactile and evaporative assessments to allow for tooth recovery. Participants with at least two eligible teeth (tactile sensitivity $\leq$ 20 g [27], an evaporative (air) Schiff $\geq$ 2 [20]) at baseline were eligible to continue in the study, and sensitivity scores for eligible teeth were recorded. Where a participant had more than two eligible teeth, those that had severe DH, ie Schiff 3, were in different quadrants and had good access were preferentially chosen.

Participants were then stratified based on the maximum baseline Schiff sensitivity score (2 or 3) across their two selected test teeth, to balance treatment groups based on initial sensitivity severity and randomised to one of the four study products using an Interactive Response Technology (IRT), non-blinded study staff carried out randomisation. To further ensure the clinical examiner remained blinded, study toothpaste tubes were overwrapped and study supplies provided in opaque bags, while dispensing was undertaken by non-blinded study staff in a separate area. All toothpastes contained 1450 ppm fluoride as sodium fluoride (NaF). The Negative control toothpaste was Colgate® Cavity Protection. Aside from the absence of absence of KNO_3 (Comparator 1) and PVM/MA (Comparator 2), Comparator 1, Comparator 2 and the test toothpaste formulations contained the exact same components at the same levels, except for the amount of silica (which was higher in Comparator 2 > Comparator 1 > Test). As well as their allocated toothpaste, participants were provided with a new manual toothbrush, timer and diary to record their twice-daily brushing. Participants were then asked to complete a supervised brushing with their assigned toothpaste, brushing their 2 selected test teeth first, followed by the whole mouth for 1 timed minute, participants were permitted to rinse with water post-brushing.

Between the Baseline and all subsequent visits participants were instructed to brush twice-daily for 1 min using their allocated toothpaste in the same way as they had during the supervised brushing, to use only the oral care products provided for the study and to record brushings in their daily diary.

2.2.3. Visit 3 - 6 (Day 3 ± 1 day, week 2 ± 1day, week 4 ± 2 days and week 8 ± 2 days)

At these visits participants first completed the DHEQ-15 [28,29], however while all questions in Section 2 were asked, in Section 1 the questions were restricted to the three questions to rate on a scale of 1 to 10: DH intensity, to what degree it is bothersome, to what degree it can be tolerated. Participants then completed the NRS [30,31]. The participants diary was reviewed for product usage compliance by non-blinded study staff. The clinical examiner then assessed DH for the two test teeth selected at baseline, starting with a tactile stimulus delivered by Yeaple probe [27], followed by an evaporative (air) stimulus assessed by Schiff [20], with a 5-min interval between assessments. Any remaining "eligible teeth" that had been identified as sensitive to both tactile and evaporative stimuli but had not been selected as the test teeth at Baseline were also assessed for evaporative sensitivity only. Participants were reminded of toothpaste instructions, and then brushed under the supervision of non-blinded study staff in a separate clinical area.

At visit 6 all study products including empty toothpaste tubes were returned to the study site by participants.

2.3. Statistical analysis

The study aimed to screen a sufficient number of participants to randomise 120 participants into treatment groups, with around 30 participants per group, a sample size of 30 evaluable participants per product group was expected to provide 95 % confidence intervals (CIs) with a precision of ±0.261 units for the Schiff sensitivity score. A sample size of approximately 30 evaluable participants per arm was also deemed sufficient to provide reliable estimates of product performance for this study and to guide the design of future clinical trials.

To assess trends in sensitivity over time (from Baseline to 8 weeks) within each product group and on inter-product comparisons, descriptive statistics were calculated as the average score of the two test teeth at each assessment time point, and change from Baseline in the modified intent-to-treat (mITT) population, stratified by study product. Raw means (±SE) of the Schiff sensitivity score at each time point were plotted for each study product across all participants in the mITT Population. In addition to the Schiff sensitivity score and the tactile sensitivity (g) and the number of sensitive teeth, were similarly summarised and plotted for the mITT population. The change in Schiff sensitivity score and tactile sensitivity (g) at Day 3 and Week 2, 4 and 8 were analysed using an analysis of covariance (ANCOVA) model that included study product as a factor and the respective baseline result as a covariate. For tactile sensitivity, the randomized stratum for Baseline Schiff sensitivity was included as an additional factor.

3. Results

This study was conducted between 28th Feb and 3rd October 2022. A total of 133 participants were screened for the study, with 132 enrolled and 120 randomised into one of four treatment groups: 29 in the test product group, 31 in each Comparator group, and 29 in the Negative control group. Of these, 118 (98.3 %) participants completed the study. Two participants (1.7 %) were discontinued: one from the Comparator 2

group due to inability to attend the final visit, and one from the Negative control group due to withdrawal of consent, Fig. 1. The majority of participants were white (86.7 %), with 7.5 % of Asian, 5.0 % Black, and 0.8 % of mixed heritage. More fs than males took part in the study (75.8 % vs 24.2 %) and the average age of the study population was 42.2 ± 13.8 years (range 18 – 65). No adverse events were reported during the study. Compliance with study administration of test products was good, from Baseline to Week 8 the mean number of brushings (± SD) was 112.0 (±0.0) in the Test, 112.03 (±0.41) in the Comparator 1, 111.83 (±0.65) in the Comparator 2, and 112.0 (±0.0) in the Negative control product group. This equated to 100 % compliance in the Test and Control groups, 97 % in Comparator 1, and 100.03 % in the Comparator 2 groups.

In the two DH test teeth selected at Baseline, mean Schiff sensitivity scores decreased significantly in all groups (Test, Comparator 1, Comparator 2, all $p < 0.001$; Negative control, $p < 0.01$) across all time points, with the test product consistently demonstrating a numerically greater reduction in Schiff sensitivity score compared to the other 3

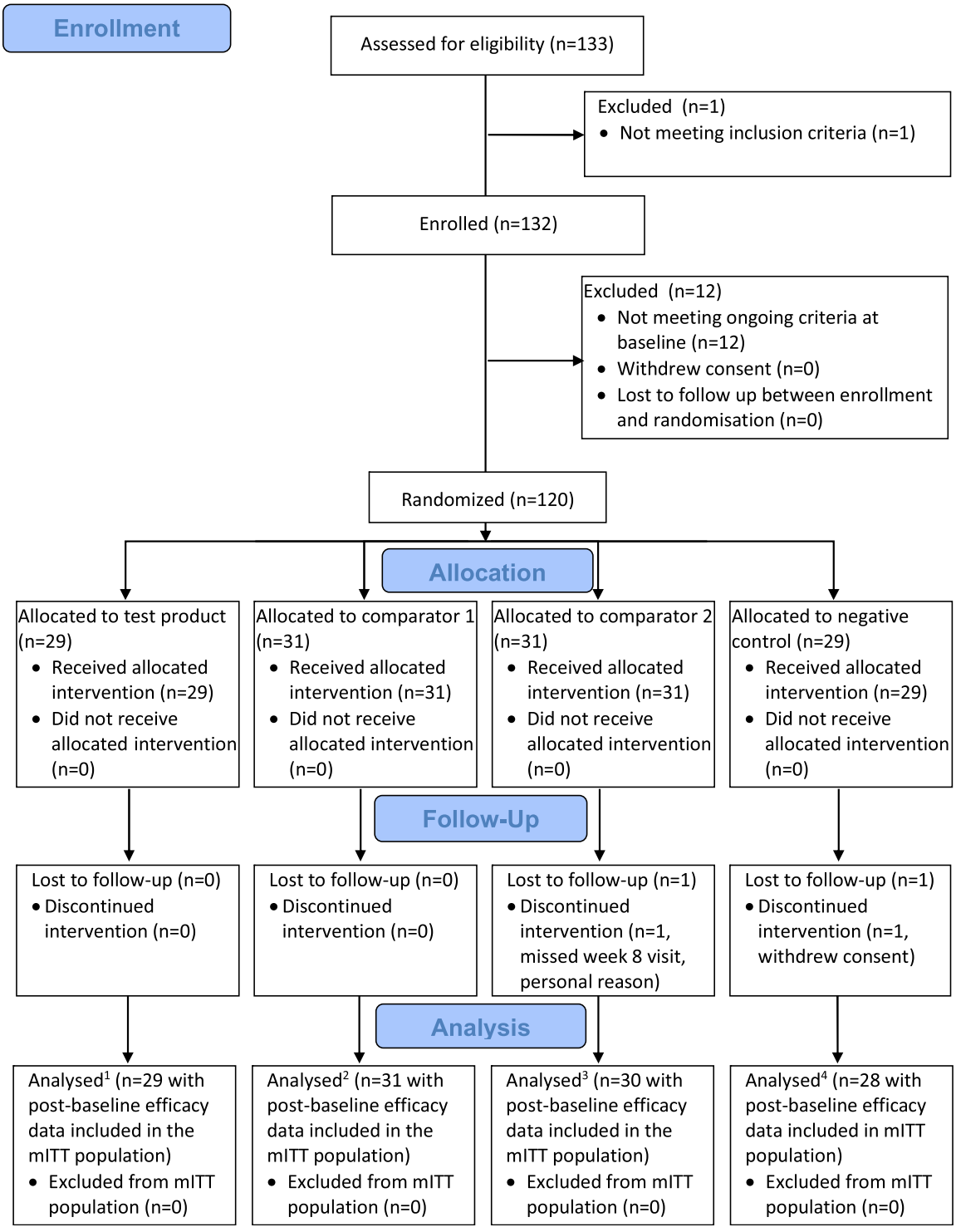

Fig. 1. Consort diagram of participant flow through the study. [1]2 participants missed week 2, and 4 missed week 4. [2]3 participants missed day 3, 2 missed week 2, and 1 missed week 4. [3]2 participants missed day 3, 1 missed week 2, and 1 missed week 4. [4]1 participant missed day 3, and 3 missed week 4.

toothpaste products (Fig. 2). Significant between group differences for these two teeth were detected at all time points except Test vs Comparator 1 at day 3 as shown in Table 1.

At Day 3 and throughout Weeks 2, 4, and 8, the mean force required to elicit a response to the tactile stimulus in the two DH test teeth selected at Baseline significantly increased across all groups ($p < 0.001$), indicating decreasing sensitivity over time. The test product showed the greatest numerical increase in tactile sensitivity in these teeth at all time points (Fig. 3). Significant between group differences in the two DH test teeth selected at Baseline were detected at all time points as shown in Table 2.

Consistent with typical phase III ADA-aligned clinical studies [32], considering 4 – 8 weeks use as the primary endpoints to demonstrate DH efficacy of toothpastes, comparisons of the test product versus each Comparator/Negative control for evaporative air Schiff score and Tactile force (Tables 1 and 2), $p = 0.0015$ was the largest p-value. With a conservative Bonferroni multiplicity adjustment (3 comparisons, 2 outcomes, 2 timepoints = 12 hypotheses) to the significance level, (0.05/12 = 0.0041) to maintain a 5 % false positive rate within these outcomes, each of these hypotheses would be rejected, showing superiority of the test product across both stimuli after 4 and 8 weeks brushing .

Responder analysis to determine clinical benefit is shown in Table 3. After 8 weeks, evaporative air Schiff score was 0 in both test teeth in significantly more participants in the Test group (> 50 % participants) as compared to the other groups (all <10 %), all $p < 0.001$.

In addition to data collected for the study's primary objective, the number of teeth remaining sensitive (Schiff score of 2 or more) were determined at each time point and reported as summary statistics. At Baseline, considering all the teeth that were eligible at Screening and Baseline (the two test teeth and those eligible but not selected as test teeth), the number of teeth with DH as elicited by evaporative air and with a Schiff score of ≥ 2 [20] for each participant was similar, with the means for each group of 3.79 (Test), 3.68 (Comparator 1), 3.68 (Comparator 2) and 3.24 (Negative control). After 8 weeks, the mean number of teeth with DH as determined by evaporative air and with a Schiff score of ≥ 2 was unchanged in the Negative control (3.25), but had fallen in the other groups, with the biggest decrease seen in the Test group with a mean of 1.72 sensitive teeth at 8-weeks.

At all time points mean self-perceived DH discomfort as measured by the NRS score decreased in those using the Test, Comparator 1 and 2 toothpastes. In contrast the mean NRS score did not decrease until weeks 4 and 8 in the Negative control group, Fig. 4. Of note, the baseline was not balanced for NRS across the groups.

At baseline DHEQ-15 scores indicated that most participants self-reported DH (82.8 % Test; 77.4 % Comparator 1, 80.6 % Comparator 2, 62.1 %, Negative control), with cold fluids being the most common trigger (range 86.2–77.4 %) with the pain most commonly lasting a few seconds (range 86.2–69.0 %). There was considerable variation between the groups in the number times per week participants experienced DH, (ranging from 51.7–27.6 % for several times a week) and the number of years they had suffered from DH, the most frequent being >5years and <20years (41.1–29.0 %). A reduction in mean DHEQ-15 scores from

Table 1
Change from Baseline to 8 weeks for Schiff sensitivity in the two DH test teeth selected at Baseline for all toothpaste treatment comparisons at all time points.

	Adjusted mean difference (SE)	95 % CI	P value
Day 3			
Test vs Comparator 1	−0.09 (0.136)	−0.36, 0.18	0.499
Test vs Comparator 2	−0.56 (0.135)	−0.83, −0.29	<0.001
Test vs Negative control	−0.83 (0.137)	−1.10, −0.56	<0.001
Week 2			
Test vs Comparator 1	−0.30 (0.112)	−0.52, −0.08	0.009
Test vs Comparator 2	−0.67 (0.111)	−0.89, −0.45	<0.001
Test vs Negative control	−1.44 (0.112)	−1.66, −1.22	<0.001
Week 4			
Test vs Comparator 1	−0.40 (0.116)	−0.63, −0.17	<0.001
Test vs Comparator 2	−0.62 (0.116)	−0.85, −0.39	<0.001
Test vs Negative control	−1.62 (0.120)	−1.85, −1.38	<0.001
Week 8			
Test vs Comparator 1	−0.36 (0.112)	−0.59, −0.14	0.002
Test vs Comparator 2	−0.83 (0.113)	−1.05, −0.61	<0.001
Test vs Negative control	−1.72 (0.115)	−1.95, −1.49	<0.001

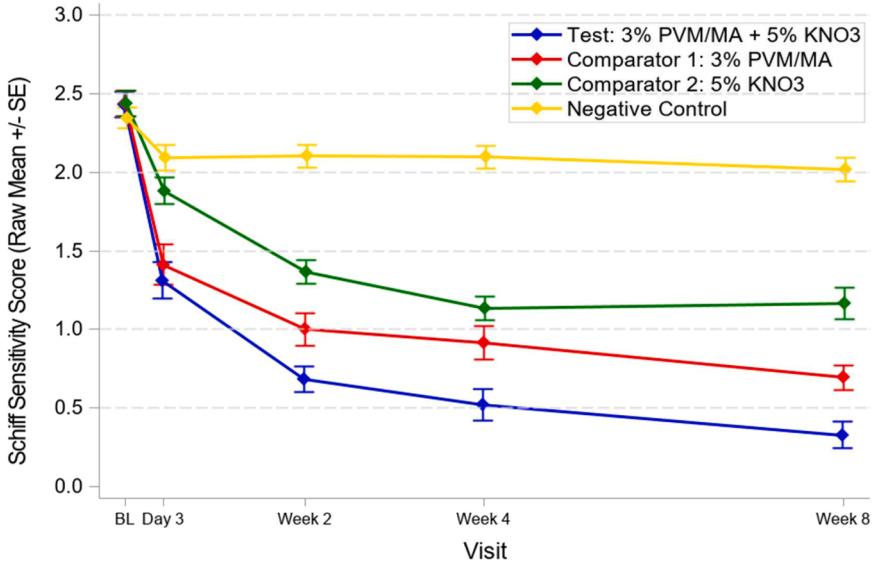

Fig. 2. Schiff sensitivity score over time in the two DH test teeth selected at Baseline.
Mean Schiff scores at Baseline for the test, Comparator 1, Comparator 2 and Negative control toothpaste groups were 2.43, 2.44, 2.44 and 2.34, respectively.

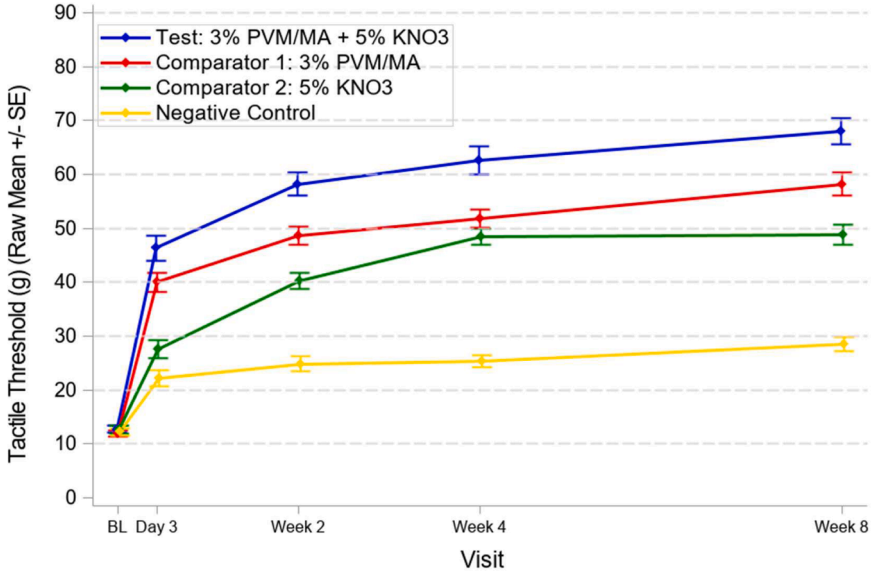

Fig. 3. Tactile sensitivity over time in the two DH test teeth selected at Baseline.
Mean tactile scores at Baseline for the Test, Comparator 1, Comparator 2 and Negative control toothpaste groups were 12.76 g, 11.94 g, 12.74 g and 12.24 g, respectively.

Table 2
Change from baseline to 8 weeks for tactile force sensitivity in the two DH test teeth selected at Baseline for all toothpaste treatment comparisons at all time points.

	Adjusted mean difference (SE)	95 % CI	P value
Day 3			
Test vs Comparator 1	5.93 (2.572)	0.83, 11.02	0.0231
Test vs Comparator 2	18.42 (2.546)	13.37, 23.47	<0.001
Test vs Negative control	23.93 (2.571)	18.83, 29.02	<0.001
Week 2			
Test vs Comparator 1	8.97 (2.293)	4.43, 13.51	<0.001
Test vs Comparator 2	17.71 (2.265)	13.22, 22.20	<0.001
Test vs Negative control	32.81 (2.288)	28.27, 37.34	<0.001
Week 4			
Test vs Comparator 1	10.20 (2.485)	5.28, 15.13	<0.001
Test vs Comparator 2	13.92 (2.460)	9.05, 18.80	<0.001
Test vs Negative control	36.51 (2.568)	31.42, 41.60	<0.001
Week 8			
Test vs Comparator 1	9.73 (2.761)	4.26, 15.20	<0.001
Test vs Comparator 2	19.06 (2.772)	13.57, 24.55	<0.001
Test vs Negative control	39.33 (2.829)	33.73, 44.94	<0.001

Table 3
Comparison with test of the percent of participants achieving a Schiff score after 4 and 8 weeks in the two DH test teeth selected at Baseline.

	Percent achieving a Schiff score					
	Week 4			Week 8		
	0	<1	≤ 1	0	<1	≤ 1
Test	36.0 %	72.0 %	88.0 %	55.2 %	86.2 %	93.1 %
Comparator 1	13.3 %*	43.3 %*	66.7 %	9.7 % ***	64.5 %	90.3 %
Comparator 2	0 % ***	20.0 % ***	56.7 % *	6.7 % ***	23.3 % ***	46.7 % ***
Negative Control	0 % ***	0 %***	3.9 % ***	0 %***	0 %***	3.6 % ***

* $p < 0.05$, *** $p < 0.001$.

baseline was generally observed across all time points, with some variations between groups. Differences between the 4 groups in the 5 DHEQ-15 domains were negligible. The baseline imbalances for DHEQ were notable.

4. Discussion

This proof-of-principle study evaluated the efficacy of a toothpaste containing both 3 % PVM/MA and 5 % KNO_3 (Test), compared with toothpastes containing 3 % PVM/MA only (Comparator 1) or 5 % KNO_3 only (Comparator 2) active ingredients, or a benchmark/Negative control fluoride toothpaste, for the management of DH. The Test toothpaste consistently demonstrated superior outcomes across both Schiff and tactile clinical measures of sensitivity for all assessments at all time points (day 3, weeks 2, 4 and 8). Further, this study demonstrated the number of sensitive teeth was relatively unchanged in the Negative control group throughout the study, but decreased in the other groups, with the biggest reduction in the number of sensitive teeth seen in the participants in the test group. Combining PVM/MA, purported to demonstrate dentinal tubule occlusion properties, with potassium nitrate, a proven DH nerve desensitising agent, provided superior and sustained relief from DH, compared to toothpastes with either PVM/MA alone, or potassium active agent alone for relief of DH.

The use of two recognised independent, stimulus-based measures of sensitivity, namely evaporative air and tactile, aligns with published guidelines for the design and conduct of DH clinical studies [33]. The results of a network meta-analysis [3] confirmed the evaporative air-blast pain measured with Schiff sensitivity scale is the most appropriate outcome measure for DH studies, with narrow confidence intervals. The second most common clinical assessment for DH in studies is the tactile/Yeaple® probe stimulus [3], however its limitations such as the need for rigorous calibration and operator to operator variability have been well documented [12]. In the present study the Yeaple probe was placed on a vibration free surface in the study clinical bay ahead of the first screening visit and remained there for the duration of the study. This environment was air conditioned to minimise the effects of changes in ambient temperature on the probe. The Yeaple probe was calibrated

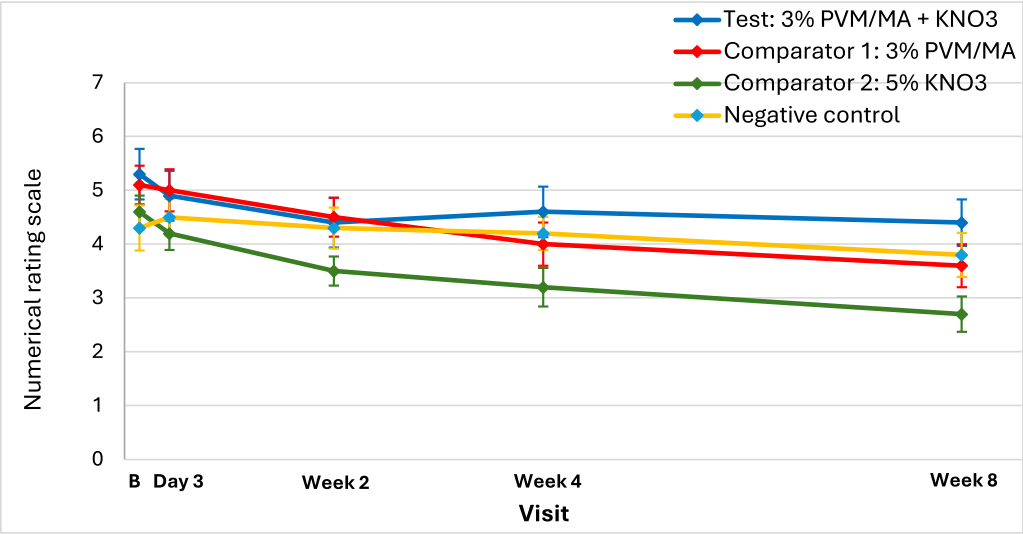

Fig. 4. Numeric rating scale over time (mITT population).
NRS ranges from 0 = no discomfort to 10 = worst discomfort imaginable.

by the same experienced study team member each morning. There was only one clinical examiner in this study thus there was no examiner to examiner variation, further the examiner was very experienced in using the Yeaple probe. Whilst recognised as a standard DH stimulus, the Yeaple stimulus does not reflect DH life experience to the same degree as cold air, as the stimulus is artificially created by repeatedly moving the probe tip across the exposed dentine surface, possibly explaining the wide confidence intervals [3]. The discrepancy in confidence intervals for the two stimuli was again manifest in this study.

According to the guidelines by [33] at least two test teeth should be selected as standard practice in sensitivity research to evaluate changes in (DH), the present study following this guidance. The study also utilised a washout period which had flexibility of between 2 and 4 weeks, however study data confirmed that all volunteers completed a very similar acclimatisation time period within this time frame. It was important to minimise differences between participants at the start of the study for standardisation, as while recent use of toothpastes formulated for DH was an exclusion criteria, non-DH oral health care products may still contain agents that are yet untested for DH but that provide some DH effect. It is possible that the exclusion of those who use DH toothpastes could have biassed recruitment towards those with less DH, however there were participants who scored the maximum Schiff score and were sensitive to the minimum Yeaple force suggesting that those with more severe DH were captured in the study. To ensure that DH intensity was as equal as possible across the groups participants were stratified by the maximum evaporative air Schiff score.

These results further align with and expand on the body of evidence to supporting both PVM/MA and KNO_3 as effective agents in DH management [2,10–12,21,22,24]. However, the combination of both PVM/MA and KNO_3 appear to offer enhanced efficacy, which has significant implications for the development of future oral care products aimed at alleviating DH.

Potassium nitrate (KNO_3) has long been established as an effective desensitising agent due to its ability to depolarise intra-dental nerves, thereby reducing the pain associated with DH [34]. In the present study, participants allocated the 5 % KNO_3 only formulation showed a statistically significant reduction in DH in their test teeth at all time points, which is consistent with previous long-term studies reporting the effectiveness of KNO_3 in DH management over 4 to 12 weeks [10–12]. By Week 8, participants in the KNO_3 only group experienced a reduction in Schiff sensitivity scores and an increase in tactile sensitivity scores, that were superior to the Negative control toothpaste. In line with the literature [10–14], the protective effect of KNO_3 (Comparator 2) was delayed compared to the occluding agent mechanism formulation, PVM/MA (Comparator 1), with marked improvements in the Comparator 2 group compared to Negative control observed only after 2 weeks use. Furthermore, the magnitude of pain relief change for Comparator 2 never reached the level of pain reduction observed in the PVM/MA alone group (Comparator 1), indicating that PVM/MA provides a faster and long-term more successful alleviation of DH pain compared to the potassium nitrate DH active agent. A large difference between the KNO_3 only toothpaste (Comparator 2) and Test toothpaste group was observed as early as Day 3, with the those allocated to the Test toothpaste showing a statistically significant reduction in Schiff sensitivity scores and tactile scores compared to the potassium only group ($p < 0.001$, both stimuli). This early effect is attributed to the faster-acting occlusion mechanism provided by PVM/MA, which complements KNO_3's desensitising action. While KNO_3 reduces nerve excitability over time, PVM/MA potentially occludes dentinal tubules more immediately, reducing fluid movement and thus decreasing the initial triggers of DH. This combined effect likely accounts for the superior outcomes of the test product.

PVM/MA has been reported to provide DH relief and it is hypothesised that this is by occlusion of the dentinal tubules, potentially reducing increased outward fluid movement on stimulation according to the hydrodynamic theory [35] and, consequently, DH symptoms [20,21]. In the present study, the 3 % PVM/MA only toothpaste demonstrated efficacy in reducing Schiff sensitivity scores and increasing tactile sensitivity, particularly after two weeks of use. These results are in line with previous findings [21], which showed that PVM/MA based toothpastes can outperform stannous fluoride in reducing DH. However, as with the KNO_3 only formulation, the PVM/MA only toothpaste did not perform as well as the Test toothpaste at any time point. The most notable difference between the PVM/MA only (Comparator 1) and Test group was observed at Week 4, when the group using the test toothpaste demonstrated a significantly greater reduction in Schiff sensitivity scores ($p < 0.001$) and tactile score ($p < 0.001$), this enhanced effect continuing to week 8 ($p = 0.002$ and $p < 0.001$, repectively)). Responder analysis demonstrated that those allocated to the Test toothpaste scored a Schiff 0 in both test teeth significantly more often than those allocated to the other toothpastes, suggesting differences between formulations yield DH relief that may be clinically relevant to patients. This suggests that while PVM/MA is effective at occluding tubules and providing relief from DH, its efficacy can be enhanced when combined with a nerve depolarisation active desensitising agent such as KNO_3. However, it

should be noted that while there were significant differences between the Test and PVM/MA group favouring the Test group at all time points, the actual difference in mean Schiff sensitivity score was never >0.4. How clinically relevant a difference of this magnitude is, depends on whether it brings DH pain below a pain threshold level, which have not definitively been defined. Both PVM/MA formulations rapidly reduced the evaporative air Schiff score indicating good efficacy, but by Week 2 the PVM/MA only toothpaste mean Schiff score was still 1 which has been taken to indicate DH [20], while it was considerably less than this for the Test formulation suggesting a clinical benefit.

The benchmark/Negative control fluoride toothpaste was included as good practice and to account for any placebo effects associated with the study design. Participants using the Negative control toothpaste showed minimal changes in Schiff sensitivity scores, tactile sensitivity, and the number of sensitive teeth. At day 3, DH did initially reduce most likely due to the placebo effect often seen in DH studies [36]. The Test paste was significantly superior at pain reduction for both clinical measurements from day 3 onwards.

At all time points the mean self-perceived DH discomfort as measured by the NRS score decreased in those using the test toothpaste, Comparator 1 and 2, whilst in contrast the mean NRS score did not decrease until weeks 4 and 8 in the Negative control group. Little meaningful interpretation can be derived from these results with confounding baseline imbalances in this proof of principle study. Similarly for the DHEQ, whilst the results are interesting for the participants as a whole, little meaningful interpretation can be gleaned again due to baseline imbalances in this proof of principle study. Furthermore the DHEQ has not been validated to assess the quality of life at shorter timepoints, which could have led to confounding results, which warrant further investigation in a bigger sample size for comparison between treatment.

The results of this study have important clinical implications for the treatment of DH. The rapid onset of DH reduction observed with the test PVM/MA and KNO_3 toothpaste suggests that patients seeking immediate relief from DH may benefit from using a product of this nature. The statistically significant improvements in both tactile sensitivity and Schiff sensitivity score by Day 3 highlight the test toothpaste's ability to provide fast and effective relief, which is a key consideration for individuals experiencing DH. Furthermore, the sustained improvement in DH observed over the 8-week period indicates that the PVM/MA+KNO_3 toothpaste not only provides immediate relief but also affords long-term benefits. This is particularly relevant in the context of patient compliance, as individuals are more likely to continue using a product that delivers both short-term and sustained pain reduction. The finding that the test toothpaste outperformed both the PVM/MA only and KNO_3 only formulations also supports the development of multi-faceted products that address multiple aspects of DH pathophysiology, tubule occlusion and nerve deactivation management strategies, maximising the potential for reducing pain and discomfort associated with DH.

4.1. Study limitations and future directions

While this study provides compelling evidence for the efficacy of the PVM/MA+KNO_3 toothpaste, several limitations should be noted. This was a single-centre study with a small sample size, not formally powered and over a relatively short duration of 8 weeks. Future research and clinical studies which includes longer-term use of the test product to assess the durability of the reduction in DH provided by the combination toothpaste, are warranted to confirm the validity of the findings reported here. The test product was not compared with toothpastes containing formulations whose effectiveness for the reduction of DH pain has been confirmed by systematic review, such as stannous, KNO_3 + stannous, or arginine [3]. For this study, the most important question was whether a product containing both active agents (KNO_3 and PVM/MA) resulted in a greater reduction in DH pain than either ingredient alone, but a study to test this combined formulation against those with proven efficacy is now warranted. Whilst the DHEQ-15 is a validated tool for assessing the impact of DH on daily life, further research is required for its use in studies with short/multiple timepoints. Importantly the baseline imbalances for DHEQ-15 and NRS were notable.

5. Conclusion

This study demonstrated that the toothpaste containing both 3 % PVM/MA and 5 % KNO_3 was the most effective in reducing clinical assessments of DH compared to toothpastes containing either active agent alone or a Negative control conventional fluoride toothpaste. The test toothpaste outperformed the single-agent formulations at all time points and all clinical assessments, supporting the hypothesis that combining PVM/MA, a purported dentinal tubule occlusion agent, with KNO_3, a proven nerve desensitising agent, provides superior and sustained relief from DH. These findings support the use of this multi-action DH management and suggest that the combination of PVM/MA and KNO_3 may represent an effective twice daily option for individuals suffering from DH.

Clinical significance statement

Daily use anti-sensitivity toothpastes are established as efficacious for the relief of DH. Inclusion of a polymer excipient may enhance clinical efficacy. As yet no universally accepted gold standard treatment has been established. This study suggests 3 % PVM/MA toothpaste, with KNO_3, warrants further investigation for managing DH.

CRediT authorship contribution statement

Joon Seong: Writing – review & editing, Writing – original draft, Methodology. **Charles Parkinson:** Writing – review & editing, Methodology, Formal analysis. **Munisha Mangal:** Writing – review & editing, Methodology, Conceptualization. **Roberta Grimaldi:** Writing – review & editing, Methodology, Conceptualization. **Gessica Serra:** Writing – review & editing, Methodology, Conceptualization. **Gary Smith:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Yashika Karandikar:** Writing – review & editing, Methodology, Conceptualization. **Nicola West:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

This study was carried out by the Clinical Trials Unit at Bristol Dental School, Bristol UK. This study was supported by Haleon, UK. CP, MM, RG, GS, GS and YK are employees of Haleon UK, a manufacturer of oral care products. NW and JS are from of Bristol contributed and declare no conflict of interest. All authors contributed towards the conceptualisation, methodology, project, administration, formal analysis of the study and reviewing & editing of the manuscript. All authors have read and agreed to the published version of the manuscript.Professor Nicola West reports financial support was provided by University of Bristol. Dr. Munisha Mangal reports financial support was provided by Haleon UK Services Limited. Dr. Munisha Mangal reports a relationship with Haleon UK Services Limited that includes: employment. Charles Parkinson reports financial support was provided by Haleon plc. Charles Parkinson reports a relationship with Haleon plc that includes: employment. Co-author is an employee of Haleon, a manufacturer of oral care products. Gary Smith reports financial support was provided by Haleon plc. Gary Smith reports a relationship with Haleon plc that includes: employment. Roberta Grimaldi reports financial support was provided by Haleon UK Services Limited. I am employee of Haleon, oral healthcare product manufacturer. If there are other authors, they declare that they have no known competing financial interests or

personal relationships that could have appeared to influence the work reported in this paper.

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