



Efficacy of an anhydrous stannous fluoride toothpaste for relief of dentine hypersensitivity: A randomized clinical study

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Abstract

Aim: To compare efficacy of an anhydrous 0.454% w/w stannous fluoride/sodium fluoride toothpaste (Test) versus a sodium monofluorophosphate toothpaste (Negative control) and a stannous chloride/sodium fluoride toothpaste (Positive control) for dentine hypersensitivity relief after 8 weeks' twice-daily use.

Materials and Methods: In this randomized, examiner-blind, stratified, parallel study, primary and secondary efficacy variables were mean changes in Schiff score (evaporative [air] sensitivity) and tactile threshold (Yeaple probe), respectively, from baseline to Week 8 between Test ($n = 62$) and Negative control ($n = 62$). Test and Positive control ($n = 61$) comparisons were exploratory objectives.

Results: All groups significantly improved from baseline on both dentine hypersensitivity measures ($p < .0001$). Difference between adjusted mean changes from baseline in Schiff sensitivity scores at Week 8 for Test versus Negative control groups was 0.19 (95% CI 0.002, 0.374), in favour of the Negative control ($p = .0476$; 12.57% difference). Difference in tactile threshold was -7.20 g (95% CI -16.376 , 1.975), and this was not statistically significant ($p = .3715$; -21.83% difference). Test group showed no significant difference versus Positive control for either measure. Toothpastes were generally well tolerated.

Conclusion: While twice-daily use of Test toothpaste significantly reduced dentine hypersensitivity from baseline, there was no significant advantage over negative or positive controls. Study registration: Clinicaltrials.gov; NCT03310268.

KEYWORDS

dentifrice, dentine sensitivity, pain, Stannous fluoride, toothpaste

1 | INTRODUCTION

Dentine hypersensitivity (DH) is a common condition that can significantly impact an individual's ability to eat, drink and brush their teeth, or participate in social interactions (Gibson et al., 2010). Individuals may report short, sharp pain or sensitivity. Differential

diagnosis is confirmed after clinical examination and exclusion of other dental pathologies (Absi, Addy, & Adams, 1987; Addy, 2000). The aetiology of the condition is linked to dentine exposure, commonly following gingival recession or enamel loss. The hydrodynamic theory is currently the accepted mechanism for DH-related pain (Brännström, 1962).

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A meta-analysis of 56 studies from around the world, involving 73,669 participants, estimated the prevalence of DH to be around 10%. However, the range in these studies varied from 1.3% to 84%, partially due to data collection differences (Cunha-Cruz & Wataha, 2015). In China, where this study took place, it is estimated that between 25% and 34% of the population experience DH (Kehua et al., 2009; Liang, Wei, Hu, & Ruan, 2017; Lin et al., 2011; Que et al., 2013; Que, Ruan, Fan, Liang, & Hu, 2010; Rong et al., 2010; Wang, Que, Lin, Hu, & Li, 2012; Ye, Feng, & Li, 2012). Assessment of the impact of DH using the Dentine Hypersensitivity Experience Questionnaire showed that participants from China with greater severity of DH had poorer oral health-related quality of life (He & Wang, 2015; He, Wang, & Wang, 2012), in line with similar studies in other countries (Basaran & Celik, 2018; Douglas-De-Oliveira et al., 2018; Gibson et al., 2010).

Twice-daily use of a sensitivity relief toothpaste is a recommendation for management of DH (Bae, Kim, & Myung, 2015). One study in China found that nearly 70% of affected individuals with DH had tried a sensitivity relief toothpaste (Kehua et al., 2009). The clinical efficacy of toothpastes containing 0.454% w/w stannous fluoride (SnF_2) for DH relief has been demonstrated in a number of randomized controlled clinical trials (He, Barker, Qaqish, & Sharma, 2011; He, Chang, et al., 2011; He, Cheng, Biesbrock, Chang, & Sun, 2011; Makin, 2013; Ni, He, Chang, & Sun, 2010; Parkinson et al., 2013; Parkinson, Jain, et al., 2015; Parkinson, Jeffery, Milleman, Milleman, & Mason, 2015; Parkinson, Nehme, Horton, Hara, & Zero, 2016; Schiff, He, Sagel, & Baker, 2006).

The primary objective of this study was to compare efficacy of 8 weeks' twice-daily brushing with a 0.454% w/w SnF_2 and sodium fluoride (NaF) toothpaste ("Test") with a regular fluoride (sodium monofluorophosphate [SMFP]) toothpaste ("Negative control") in individuals with DH, as measured by response to evaporative (air) stimulus (Schiff score). The secondary objective was comparison of response to a tactile stimulus (Yeaple probe) at 8 weeks. Exploratory objectives included comparing Test toothpaste with a sensitivity toothpaste containing stannous chloride (SnCl_2) and NaF ("Positive control"), using evaporative (air) and tactile stimuli, after 8 weeks and all comparisons at 4 weeks. The Positive control comparison was not carried out as a primary/secondary objective as efficacy of this toothpaste has already been shown (Ni et al., 2010), and as both Test and Positive control toothpastes contained the same levels of stannous and fluoride as the active ingredients, no differences were expected clinically.

2 | MATERIALS AND METHODS

2.1 | Study design

This was an 8-week, randomized, controlled, stratified, examiner-blind, three-treatment, parallel-group clinical trial. The study was conducted in China, in full compliance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, good clinical practice regulations, applicable participant privacy requirements and the

Clinical Relevance

Scientific rationale for the study: Stannous fluoride (SnF_2)-containing toothpastes have been shown to be effective in relieving dentine hypersensitivity (DH) with twice-daily use. The transient episodic nature of DH as a condition may require further evaluation.

Principal findings: Eight weeks' twice-daily brushing with a SnF_2 /sodium fluoride "Test," a stannous chloride/sodium fluoride "Positive control" or a sodium monofluorophosphate "Negative control" toothpaste delivered DH relief in all three groups.

Practical implications: This study supports SnF_2 toothpaste effectiveness in managing DH; however, the SnF_2 toothpaste showed no significant advantage over the negative or positive controls for DH relief.

ethical principles outlined in the Declaration of Helsinki. The Clinical Study Ethics Committee of the Shanghai Ninth People's Hospital approved the protocol [2017-377-C36]; the trial was registered at clinicaltrials.gov (#NCT03310268). Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

2.2 | Participants

Eligible participants were aged 18–70 years and in good general and oral health with a self-reported DH history of 6 months to 10 years. Exclusion criteria included any acute or chronic condition that could interfere with study results or be exacerbated by the study; taking any medication/treatment likely to cause xerostomia or provide pain relief; and allergy/intolerance to study ingredients and antibiotics intake within 2 weeks of screening/baseline or during the study and history (1 year) of alcohol or other substance abuse. Inclusion criteria were presence of ≥ 20 natural teeth, including two accessible non-adjacent teeth (incisors, canines or pre-molars) with diagnosed sensitivity at baseline and screening; a tactile stimulus threshold of ≤ 20 g (Polson, Caton, Yeaple, & Zander, 1980) and a Schiff Sensitivity Scale score of ≥ 2 (Schiff et al., 1994; see below for details). Eligible teeth had a clinical mobility score of ≤ 1 (Laster, Laudenbach, & Stoller, 1975) with cervical erosion, abrasion, and/or gingival recession (EAR) on buccal surfaces and a Modified Gingival Index score adjacent to the test teeth area (exposed dentine) of 0 (Lobene, Weatherford, Ross, Lamm, & Menaker, 1986).

Participants with any tongue or lip piercing or dental implants were excluded. In addition, presence of periodontal disease or treatment of periodontal disease (including surgery) within 12 months; scaling or root planing within 3 months; teeth whitening or desensitizing treatment (including over-the-counter products) within 8 weeks; dental prophylaxis within 4 weeks; or participation in

another clinical study or use of any investigational drug within 30 days of screening were excluded.

Exclusions for teeth tested for DH included: not expected to respond to an over-the-counter DH relief toothpaste (in the investigator's opinion); presence of deep, defective or buccal restorations; full crowns or veneers; abutment teeth for dentures; orthodontic bands; cracked enamel; current/recent caries experience; or treatment for caries within 12 months of screening.

2.3 | Tooth sensitivity assessments

Tactile and evaporative (air) assessments of tooth sensitivity were performed by a single trained examiner (WY) from the study site staff. Tactile sensitivity was assessed using an electronic constant-pressure force-sensing (Yeaple) probe (Polson et al., 1980), with participants indicating whether the sensation experienced was painful. Testing began at 10 g and increased by 10 g increments until a "yes" response was recorded. Tactile threshold was recorded as the weight of force that elicited two consecutive "yes" responses. Maximum force used at screening and baseline was 20 g, and after 4 and 8 weeks, it was 80 g.

Following a 5-min interval to allow for recovery, teeth assessed by tactile threshold were re-evaluated by an evaporative (air) stimulus. The same examiner isolated the affected tooth surface and directed a 1-s air blast from approximately 1 cm distance onto exposed dentine. The participant's response was assessed using the 4-point Schiff Sensitivity Scale (from 0: participant did not respond, to 3: participant responded to stimulus, considered it painful, and requested discontinuation; Schiff et al., 1994).

2.4 | Clinical procedures and study toothpastes

At screening, participants gave written informed consent to participate in the study. Full oral hard- and soft-tissue examinations were conducted. Eligible participants were dispensed with a fluoride-only toothpaste (1,400 ppm fluoride as SMFP; Colgate® Strengthen Fresh; Colgate-Palmolive Co; China-marketed product) and toothbrush (Aquafresh® Clean Control; GSK Consumer Healthcare, Brentford, UK-marketed product) for use during the acclimatization period between screening and baseline visits. First use was carried out under supervision by study site staff not involved in the clinical assessments.

The baseline visit was 2–3 weeks after screening. Acclimatization regimen adherence was assessed by study site staff not involved in the clinical assessments using participant-completed diaries. An oral soft-tissue examination was performed by the examiner followed by assessment of all eligible teeth (incisors, canines, pre-molars), as above, by tactile then evaporative (air) assessment for DH. Of those teeth diagnosed with DH, two "test teeth" were selected for use in the study at the discretion of the examiner, as long as they were non-adjacent to each other. Where possible, test teeth were selected from different quadrants.

Participants were stratified, by study site staff not involved in the clinical assessments, by maximum baseline Schiff sensitivity score (2 or 3) of the test teeth and randomized to one of three study toothpastes in a 1:1:1 ratio according to a schedule generated by a contract research organization using validated internal software (SAS version 9.4; SAS Institute Inc.). Study toothpastes were as follows:

- Test toothpaste containing 0.454% w/w SnF₂ and 0.072% w/w NaF (1,450 ppm fluoride);
- Negative control toothpaste containing SMFP (1,400 ppm fluoride; Colgate® Triple Protection; Colgate-Palmolive Co; China-marketed toothpaste);
- Positive control toothpaste containing SnCl₂ and 0.15% w/w NaF (1,450 ppm fluoride; Crest® 7-Effects Strengthen Dental Enamel; Procter & Gamble Co; China-marketed toothpaste).

Toothpaste tubes were over-wrapped in white vinyl to blind participants to allocation. The examiner, study statistician, data management staff and sponsor employees were blinded to treatment allocation.

Participants applied a ribbon of their assigned toothpaste to cover the head of the toothbrush and brushed their teeth in their usual manner for 1 timed minute twice daily (using a supplied timer), morning and evening. First use was carried out under supervision at the study site; participants recorded each brushing in a provided diary. The toothbrush was replaced at Week 4.

Participants returned to the study site at Weeks 4 and 8. Adherence to the study regimen was reviewed based on participant diaries. Any adverse events (AEs) were reported from first use of the acclimatization toothpaste through to the end of the study. At assessments, after a full oral soft-tissue examination, sensitivity of the two test teeth was evaluated by tactile and evaporative (air) assessments. Participants were asked to refrain from eating and drinking for at least 4 hr prior to study visits, except for small sips of water up to 1 hr prior to assessments. Participants were to refrain from excessive alcohol consumption for 24 hr prior to baseline, Week 4 and Week 8 visits.

2.5 | Statistical analysis

Sufficient participants were screened so that approximately 180 could be randomized to treatment, ensuring 165 (approximately 55 per treatment group) completed the Week 8 assessment. It was determined that this sample size would provide 80% power (two-sided two-sample *t* test of 0.05) to detect a mean treatment difference of 0.33 [standard deviation (SD) of 0.619] in change from baseline in Schiff sensitivity score at 8 weeks (based on a previous study, data on file).

The safety population included all randomized participants who received at least one dose of study toothpastes. The efficacy analysis was performed on a modified intent-to-treat (mITT) population, defined as all participants who received the study treatment and had at least one post-baseline efficacy measurement. The per protocol

population included all participants who were assessed as sufficiently compliant with study procedures and restrictions.

The primary and secondary efficacy variable analysis was comparison of mean change from baseline in Schiff sensitivity score and tactile threshold, respectively, between Test and Negative control toothpaste groups at Week 8. The change from baseline was derived from the individual teeth first, before calculating the average change of the two test teeth per participant. Exploratory analyses included all these comparisons at Week 4 and between Test or Negative control and Positive control groups at Weeks 4 and 8.

Statistical analyses were performed using analysis of covariance (ANCOVA) with treatment as a factor and the appropriate mean baseline score (Schiff sensitivity score or tactile threshold) as a covariate. Baseline Schiff stratification value was included as a factor for tactile threshold analyses. The assumption of normality and homogeneity of variance in the ANCOVA model was investigated and, if violated, data transformations and non-parametric techniques were investigated.

3 | RESULTS

3.1 | Participants

Study flow is shown in Figure 1. The first participant was enrolled in November 2017; the final participant completed the study in February 2018. Of the 688 participants screened, 185 were randomized to treatment and were included in the safety population with 179 participants (96.8%) completing the study. Two participants in the Negative control toothpaste group did not have any post-baseline assessments performed and were excluded from the mITT population. Participants were aged between 20 and 64 years [mean (SD): 39.9 (9.94) years]; the majority were female (87%). Most participants (70.8%) had a maximum baseline Schiff score of 2. Baseline characteristics were well balanced between treatment groups (Table 1).

3.2 | Efficacy

At Weeks 4 and 8, adjusted mean decreases from baseline in Schiff sensitivity score and increases in tactile threshold was seen, both

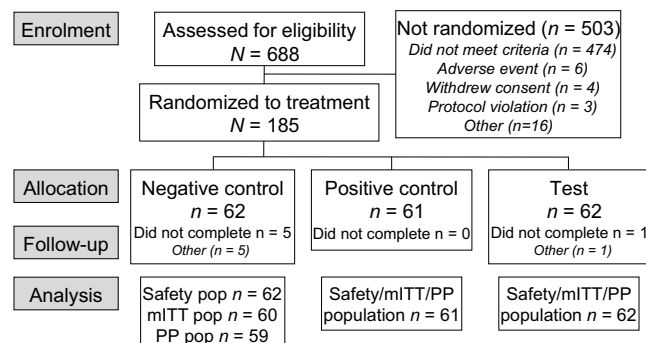


FIGURE 1 Study flow

indicating a reduction in DH. These were statistically significant ($p < .0001$) in all three treatment groups, for all evaluations (Figures 2 and 3; Table 2).

When comparing Test and Negative control groups, the difference between adjusted mean change from baseline in Schiff sensitivity scores at Week 8 was 0.19 [95% confidence interval (CI) 0.002, 0.374], representing a 12.6% percentage difference in the observed raw means. This was statistically significant in favour of the Negative control group ($p = .0476$; Table 3). At Week 4, the Test and Negative control groups were not significantly different.

When Positive and Negative control groups were compared, the result showed a significant difference in Schiff sensitivity scores in favour of the Negative control at both 4- and 8-week timepoints ($p < .05$; Table 3). There were no significant differences at either timepoint between the Test and Positive control groups for Schiff sensitivity scores.

Difference between adjusted mean change from baseline in tactile threshold at Week 8 for the Test group compared with the Negative control group was -7.20 (95% CI $-16.376, 1.975$; 21.83% difference in observed raw means); this was not statistically significant (Table 3). No significant differences were shown between the Positive control and either the Test or Negative control groups at either timepoint (Table 3).

3.3 | Safety

There were 17 treatment-emergent AEs (TEAEs) reported by 14 participants (7.6%). Ten of these TEAE were oral, six in the Test group (lip ulceration [$n = 3$], oral herpes, mouth ulceration, non-infective gingivitis), one in the Negative control group (oral herpes), three in the Positive control group (oral herpes, angular cheilitis, pulpitis dental). Specific TEAEs are not reported as none were considered treatment-related; all had resolved upon study completion. There were no serious AEs reported, and no participants discontinued study treatment or withdrew from the study because of a TEAE.

4 | DISCUSSION

The global prevalence of DH appears to be increasing, at least partly due to longer retention of natural dentition and a possible increase in the incidence of tooth erosion (Olley & Sehmi, 2017). In China, where this study took place, it is estimated that at least one in four people experiences tooth sensitivity (Kehua et al., 2009).

This study was designed to evaluate efficacy of an anhydrous 0.454% w/w SnF₂ + NaF toothpaste in participants with DH compared with a fluoride-only Negative control toothpaste and a SnCl₂ + NaF Positive control. The results showed that all groups improved in both measures of DH experience, including the Negative Control group. According to criteria set out by Orchardson, Gangarosa, Holland, and Pashley (1994), a clinically meaningful difference from baseline would be a change of at least 33%. For all

	Test (n = 62)	Negative control (n = 62)	Positive control (n = 61)
Sex, n (%)			
Female	55 (88.7)	47 (75.8)	59 (96.7)
Male	7 (11.3)	15 (24.2)	2 (3.3)
Mean age, years (SD)	40.2 (10.83)	40.3 (9.12)	39.4 (9.95)
Stratification, n (%)			
Maximum baseline Schiff score, 2	44 (71.0)	44 (71.0)	43 (70.5)
Maximum baseline Schiff score, 3	18 (29.0)	18 (29.0)	18 (29.5)

Abbreviation: SD, standard deviation.

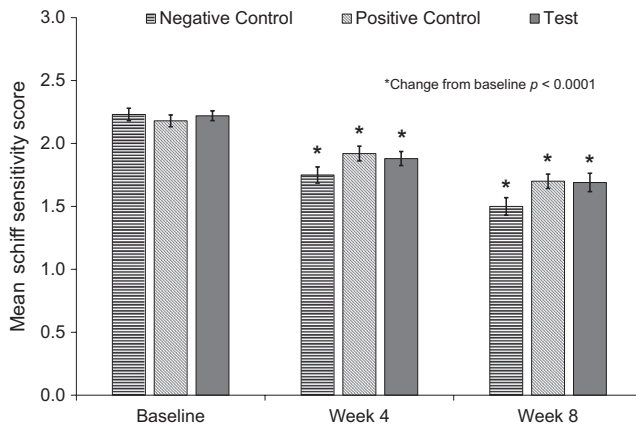


FIGURE 2 Raw mean (\pm SE) Schiff sensitivity scores at baseline, Week 4 and Week 8 according to treatment group (mITT population)

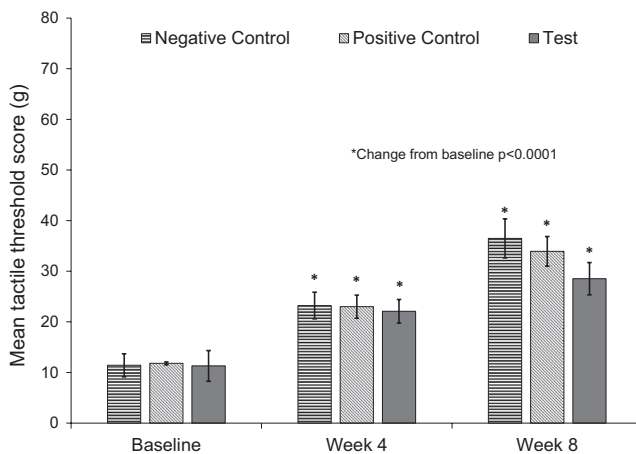


FIGURE 3 Raw mean (\pm SE) tactile threshold at baseline, Week 4 and Week 8 according to treatment group (mITT population)

three toothpastes, the change from baseline in tactile threshold was well above this level. The baseline tactile tolerances for all three groups were around 11–12 g, and after 8 weeks, all three groups could tolerate between 29 and 37 g. Of note, compared with baseline, Schiff sensitivity scores at Week 8 showed reductions of 24%

TABLE 1 Baseline demographics and characteristics (safety population)

TABLE 2 Raw mean (\pm SE) Schiff sensitivity and tactile threshold scores (mITT population)

	Test (n = 62)	Negative control (n = 60)	Positive control (n = 61)
Schiff sensitivity score: mean (\pm SE) [percentage change from baseline]			
Baseline	2.22 (0.047)	2.23 (0.050)	2.18 (0.039)
4 weeks	1.88 (0.059) [-15.3%]	1.75 (0.064) [-21.5%]	1.92 (0.056) [-11.9%]
8 weeks	1.69 (0.057) [-23.9%]	1.50 (0.070) [-32.7%]	1.70 (0.073) [-22.0%]
Tactile threshold score: mean (\pm SE) [percentage change from baseline]			
Baseline	11.13 (0.291)	11.42 (0.293)	11.80 (0.388)
4 weeks	22.08 (2.278) [98.4%]	23.22 (2.631) [103.3%]	23.00 (2.345) [94.9%]
8 weeks	28.52 (2.925) [156.2%]	36.49 (3.858) [219.5%]	33.93 (3.188) [187.5%]

Abbreviations: mITT, modified intent to treat; SE, standard error.

for Test, 22% for Positive control and 33% for Negative control. According to the Orchardson et al. criteria (Orchardson et al., 1994), only the Negative control differences from baseline would be considered clinically meaningful.

Differences in results between the two measures used in this study have been noted previously and underpin the recommendation to test at least two sensitivity measures for DH (Holland, Narhi, Addy, Gangarosa, & Orchardson, 1997). Individual participants may have varied responses to different stimuli applied to individual teeth, for instance, increased sensitivity to tactile pressure versus evaporative air (Gernhardt, 2013; Orchardson & Collins, 1987).

A number of studies on the anti-sensitivity effect of SnF₂ toothpastes have been carried out following a similar protocol to that used here, over 8 weeks. These have found significant differences between SnF₂ toothpastes and a negative control (Gallob, Sufi, Amini, Siddiqi, & Mason, 2017; He, Barker, Biesbrock, & Sharma, 2014; Hines et al., 2019; Parkinson et al., 2013; Parkinson, Jain, et al., 2015; Parkinson, Jeffery, et al., 2015; Schiff et al., 2006; Schiff, Saletta, Baker, Winston, & He, 2005) and comparable reductions compared to positive controls

TABLE 3 Between-treatment differences in change from baseline in sensitivity assessments (mITT population)

	Mean between-treatment difference [95% CI] ^a	<i>p</i> -Value ^b	% difference (observed raw means) ^c
Schiff sensitivity score			
Week 4			
Test vs. Negative control	0.15 [-0.012, 0.312]	.0692	7.9
Test vs. Positive control	-0.04 [-0.207, 0.117]	.5844	-2.1
Positive control vs. Negative control	0.20 [0.032, 0.358]	.0192	
Week 8			
Test vs. Negative control	0.19 [0.002, 0.374]	.0476	12.6
Test vs. Positive control	-0.02 [-0.202, 0.162]	.8411	-0.5
Positive control vs. Negative control	0.21 [0.020, 0.393]	.0298	
Tactile threshold, g			
Week 4			
Test vs. Negative control	-0.16 [-6.435, 6.122]	.9608 [0.9888]	-4.9
Test vs. Positive control	1.18 [-5.104, 7.470]	.7108 [0.6586]	-4.0
Positive control vs. Negative control	-1.34 [-7.616, 4.937]	.6741 [0.6832]	
Week 8			
Test vs. Negative control	-7.20 [-16.376, 1.975]	.1232 [0.3715]	-21.8
Test vs. Positive control	-4.04 [-13.099, 5.011]	.3793 [0.2598]	-15.9
Positive control vs. Negative control	-3.16 [-12.330, 6.017]	.4979 [0.9754]	

Abbreviations: CI, confidence interval; mITT, modified intent to treat.

p-values in bold are statistically significant.

^aFrom ANCOVA model. Difference is first named treatment minus second named such that a negative difference favours first named for Schiff sensitivity score and a positive difference favours first named for tactile threshold.

^b*p*-Value from ANOVA; as the underlying assumption of normality and homogeneity of variance was slightly violated, supportive non-parametric analysis *p*-value appears in square brackets (van Elteren test adjusting for the maximum baseline Schiff sensitivity scores).

^cPercentage calculated as $100 \times (\text{Test toothpaste} - \text{control})/\text{control}$.

(Ni et al., 2010). In this current study, while there were significant improvements in DH measures, the primary and secondary objectives were not met as the differences from baseline between Test versus Negative control toothpaste was in favour of the latter for Schiff sensitivity score (with no significant difference at 4 weeks) and was not significant for tactile threshold (at both timepoints).

The Negative control toothpaste chosen in this study did not contain any ingredients known to impact DH. The results of this clinical study warrant some further exploration. With regard to the differences from baseline seen in the Negative control group in this study, a Hawthorne effect may have been observed simply due to participation in the study, leading to a change in DH experience (Benedetti, Carlino, & Piedimonte, 2016; West, Addy, Jackson, & Ridge, 1997). As with all pain studies, a placebo effect may have also played a part (Benedetti et al., 2016; Kirsch, 2013; West et al., 1997). This is a known phenomenon in DH studies with between 20% and 60% of treatment effects estimated to be due to a placebo response (West et al., 1997). Although participants were only eligible if they had experienced DH for at least 6 months, it may also be that for some participants, DH symptoms lessened by themselves during the study, as it is known to be episodic in nature (West et al., 1997).

Another possible limitation is that while the identity of the toothpastes was concealed, there were some differences in taste and texture of the toothpastes, with some potential implications on personal preference and compliance. Again, this is a limitation accepted in many similar toothpaste studies. A final limitation may be that oral hygiene procedures were not standardized or controlled, just duration of brushing. Further studies may need to consider being more prescriptive about brushing duration and extent of rinsing while or after brushing teeth so as to have all participants using comparative oral hygiene procedures.

This study highlights the inherent complexities of measuring and recording pain, particularly given the intermittent nature of DH. In addition, DH is incited and then measured in the dental chair by the examiner. Further studies could include more detailed patient-reported outcomes. This study also shows the findings versus a Positive control, together with the perceived beneficial impact of the Negative control on DH experience. We believe negative outcomes of studies conducted according to established, standardized methodologies are valuable to better our understanding of the condition and its effective management and convey further exploration of DH experience by individuals.

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CONFLICTS OF INTEREST

ML, AS and AA are employees of GSK Consumer Healthcare, who provided funding for this study. DT, XF and WY are employees of Shanghai Jiao Tong University, and JG is an employee of Consumer Research Consulting, both of which received funding from the study sponsor.

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