Evaluation of two different remineralising toothpastes in children with drug-controlled asthma and allergic rhinitis: a randomised clinical trial

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Abstract

Aim To compare the efficacy of two remineralising toothpastes in children suffering from asthma and allergic rhinitis after a 6-month study.

Study design Single-center, parallel, active-controlled randomised clinical trial with 1:1 allocation ratio. Trial registration: NCT05631197.

Methods 40 patients aged between 6-14 years with enamel demineralisations were enrolled for the study at the Unit of Dental Hygiene of the University of Pavia (Italy). The following indices were collected: Schiff air index (SAI), plaque index (PI), bleeding on probing (BoP), salivary pH, Basic Erosive Wear Examination (BEWE), susceptibility index (SI) for hard and soft tissues' pathologies, and decayed missing filled teeth (DMFT). After mechanical debridement with piezoelectric instrumentation and glycine powder, patients were equally divided into two groups: Group 1 using a toothpaste with zinc hydroxyapatite, and Group 2 using a toothpaste containing calcium sodium phosphosilicate. The toothpaste had to be used twice a day. The time frames of the study were: baseline (T0), after 1 month (T1), after 3 months (T2), after 6 months (T3).

Results PI, BoP, SAI were significantly reduced in both the Groups after the 6-month treatment ($p<0.05$), with no significant intergroup differences ($p>0.05$). SI resulted to be significantly reduced in Group 1 from T2 to T3 ($p<0.05$), while the same did not happen for Group 2 ($p>0.05$) and no intergroup differences were found ($p>0.05$). Salivary pH, DMFT and BEWE did not exhibit inter- and intragroup significant differences ($p>0.05$).

Conclusions The tested toothpastes can be proposed for home use in children with asthma and allergic rhinitis as they significantly reduced dental sensitivity and periodontal indices.

KEYWORDS Asthma, allergic rhinitis, paediatric patients, remineralising treatment, dental sensitivity, periodontal health, zinc hydroxyapatite, calcium sodium phosphosilicate, respiratory complications.

Introduction

Among respiratory disorders in children, allergic rhinitis and asthma are diffusely widespread among all the populations of the world, with an increasing prevalence in industrialised countries [GBD Chronic Respiratory Disease Collaborators, 2020].

Asthma is the most common non-communicable disease in paediatric patients, with an increasing global prevalence of 14% [Zar et al., 2014]. Generally, patients present a triad of symptoms, in detail wheeze, shortness of breath and cough [Martin et al., 2022]. Allergic rhinitis, instead, consists of a mucosal inflammation of the nasal epithelia elicited by Immunoglobulin E (IgE)-mediated responses to the contact of inhaled allergens, causing nasal congestion, sneezing, rhinorrhea, and nasal itching. The prevalence can be up to 50% in high-income countries [Bousquet et al., 2020]. Generally, the two diseases are related as approximately 30% of patients with rhinitis develop asthma and up to 80% of patients with asthma have rhinitis [Bousquet et al., 2016]. Studies show that children with asthma and allergic rhinitis exhibit higher scores of periodontal inflammation and plaque accumulation [Vitale et al., 2023] and are prone to exhibit developmental defects of enamel [Samec et al., 2022]; moreover, dental caries can be causal factor of asthma according to a recent systematic review with meta-analysis, suggesting a non-univocal relationship between the two entities known the microbiological background [Zhai et al., 2023]. Additionally, pharmacological approaches for asthma, among which anticholinergics, inhaled corticosteroids, and beta$_2$-agonists, have been found to cause salivary alterations and changes in oral and periodontal health [Thomas et al., 2010], even though in children conflicting results have been obtained [Nørrisgaard et al., 2023; Świątkowska-Bury et al., 2022]. Asthmatic patients often take inhaled corticosteroids, and they have been shown to cause enamel demineralisation [Rizzardi et al., 2022], while in soft tissues they can cause dry mouth and oral candidiasis [Pacheco-Quito et al., 2023]. Nonetheless, it should be considered that the level of evidence

of recent systematic reviews investigating oral health in children suffering from those pathologies is defined as very low [Moreira et al., 2023; Calvo-Henriquez et al., 2023], therefore further research should be aimed at performing novel clinical studies to deepen the topic. Various treatments could be tested in paediatric patients for the improvement of hard and soft-tissue health, among which ozonised water [Cosola et al., 2019] and low-level laser therapy [da Silva et al., 2022], but the additional evaluation of home products to be used daily would be desirable as an alternative to in-office procedures. To the knowledge of the Authors, no previous study assessed the efficacy of domiciliary aids for the improvement of the oral hygiene level of children suffering from these conditions, therefore the present study aimed to compare the efficacy of two different remineralising typologies of toothpaste in a 6-month domiciliary trial for the reduction of dental sensitivity and the improvement of dental and periodontal conditions in children suffering from asthma and allergic rhinitis. The null hypothesis was that no significant difference was found between the two groups regarding the variables of the study over time.

Materials and Methods

Trial design

The present study was a single-centre, parallel, active-controlled randomised trial with an equal number of patients allocated in the two study groups. The Unit Internal Review Board approved the study (ID: 2022-0202) and trial registration was provided on the clinicaltrials.gov platform (NCT n°: NCT05631197).

Participants

The study was performed at the Unit of Dental Hygiene, Section of Dentistry, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences of the University of Pavia, 27100 Pavia, Italy. The beginning of the study was in March 2022, and it ended in September 2023. Written informed consent was obtained from patients for participation in the study. Patients were selected among children attending for regular care the Pediatric Clinic of the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy for asthma and allergic rhinitis. The following inclusion criteria were adopted for the enrollment of the patients: i) paediatric patients aged between 6-14 years, ii) diagnosis of allergic rhinitis and asthma, iii) controlled asthma and/or allergic rhinitis with drug therapy, iv) diffused enamel demineralisations of deciduous and permanent teeth. The following exclusion criteria were adopted: i) low cooperation according to grades 3 and 4 of the Frankl behavioural scale, ii) nonadherence to the study protocol checked by parents, iii) other systemic diseases.

Interventions and outcomes

At the baseline (T0), patients were visited and underwent an oral examination performed by an experienced calibrated operator. The following indices were recorded to assess periodontal and hard tissues health: Schiff air index (SAI) [Arshad et al., 2021]; plaque index (PI) [Giuca et al., 2015]; bleeding on probing (BoP) [Giuca et al., 2015]; salivary pH, assessed with pH test strips (Just Fitter Pty Ltd, Ashmore Queensland, Australia) inserted for 15 seconds inside a glass with the patient's saliva; basic erosive wear examination (BEWE) [Marqués Martínez et al., 2019]; susceptibility index (SI) for hard and soft tissues' pathologies assessed as mild (6.7< pH <7.8, BEWE 0-1, SAI 0-1), moderate (6.0 <pH <6.6, BEWE 1-2, SAI 1-2), and severe (pH <6.6, BEWE 2-3, SAI 2-3); decayed missing filled teeth (DMFT) [Costacurta and Docimo, 2020]. A periodontal probe (UNC probe 15; Hu-Friedy, Chicago, IL, USA) was used for the assessment of periodontal indices. Subsequently, a nonsurgical mechanical periodontal debridement was performed by the calibrated operator, using a piezoelectric instrument (Multipiezo, Mectron S.p.a., Carasco, Italy) and glycine powders with a specific handpiece (Mectron S.p.a.), with careful attention in saliva ejection for the dispersion of the powders. Patients were instructed to proper oral hygiene manoeuvres with a soft-bristled toothbrush and then randomly subdivided into two groups, according to the products that had to be used for the domiciliary protocol:

- in Group 1, a toothpaste containing biomimetic hydroxyapatite (Biorepair Total Protection Plus®, Coswell S.p.A., Funo di Argelato, BO, Italy) used for 2 minutes during brushing plus Desensitizing enamel-repair shock treatment® used for 1 week per month for all the duration of the study, applied for 10 minutes with a provided appliance;
- in Group 2, instead, a toothpaste containing calcium sodium phosphosilicate (Sensodyne Repair&Protect, Haleon Italy S.r.l., Milan, Italy) was used for 2 minutes during brushing.

The composition of the toothpastes is presented in table 1. The time frames of follow-up visits were after 1 month (T1), after 3 months (T2) and after 6 months (T3), in which the periodontal indices were re-evaluated, and another

Product	Manufacturer	Composition
Biorepair Total Protection Plus ®	Coswell S.p.A., Funo di Argelato, BO, Italy	Aqua, Zinc Hydroxyapatite (microRepair®), Glycerin, Sorbitol, Hydrated Silica, Silica, Aroma, Cellulose Gum, Tetrapotassium Pyrophosphate, Sodium Myristoyl Sarcosinate, Sodium Methyl Cocoyl Taurate, Sodium Saccharin, Citric Acid, Phenoxyethanol, Benzyl Alcohol, Sodium Benzoate.
Biorepair Desensitizing enamel-repair shock treatment®	Coswell S.p.A., Funo di Argelato, BO, Italy	Aqua, Zinc Hydroxyapatite (microRepair®), Hydrated Silica, Silica, Sodium Myristoyl Sarcosinate, Sodium Methyl Cocoyl Taurate, Sodium Bicarbonate, Aroma, Sodium Saccharin, Phenoxyethanol, Benzyl Alcohol, Sodium Benzoate, Citric Acid, Menthol.
Sensodyne Repair&Protect®	Haleon Italy S.r.l., Milan, Italy	Glycerin, PEG-8, Hydrated Silica, Calcium Sodium Phosphosilicate (Novamin®), Cocamidopropyl Betaine, Sodium Methyl Cocoyl Taurate, Flavour, Titanium Dioxide, Carbomer, Sodium Fluoride, Sodium Saccharin, Limonene.

TABLE 1 Products used in the study.

mechanical debridement was performed.

Sample size

The sample size was calculated considering alpha = 0.05 (type I error) and power = 80% (type II error) for two independent study groups. Schiff Air Index was considered as the primary outcome, therefore an expected mean of 1.18 and an expected difference between the means was supposed to be 0.64 with a standard deviation of 0.72 [Arshad et al., 2021]; the definite number of patients for the study was therefore 40, equally divided into the two study groups.

Randomisation and Blinding

The data analyst used a block randomisation table for the generation of the random sequence considering a permuted block of 40 patients. The allocation was performed with sequentially numbered, opaque, sealed envelopes; afterwards, the calibrated operator performed the mechanical periodontal debridement, while the care provider assigned patients to Group 1 or Group 2. Patients, operators, and data analysts were blinded for allocation. As regards the domiciliary protocol, the products were concealed.

Statistical Methods

R Software (R version 3.1.3, R Development Core Team, R Foundation for Statistical Computing, Wien, Austria) was used to perform statistical analysis. Mean and standard deviation for all the variables were calculated as descriptive statistics. Data normality of distributions was analysed with Kolmogorov–Smirnov test, followed by Friedman non-parametric. In presence of the significance of Friedman test, Dunn's post hoc test was performed for multiple comparisons. A significance threshold of $p < 0.05$ was set for all the statistical tests.

Results

Participant Flow and Baseline Data

Patients were recruited until 40 participants were enrolled. Patients were allocated into two groups. All the patients concluded the study and data were analysed (figure 1). At the beginning of the study, patients exhibited a mean age of 9.8 ± 2.4 years (23 males and 17 females). For Group 1, the mean age was 9.3 ± 2.4 years (8 males and 12 females), while for Group 2 it was 10.4 ± 2.5 years (15 males and 5 females). Figure 1 presents the entire flow of the study. Patients were taking various therapeutic medications to control asthma and/or allergic rhinitis (Table 2).

Outcomes

To highlight significant differences among the variables of the study, multiple comparisons were denoted with a letter-based notation, which that means with same superscript lowercase letters do not show statistical significance [Piepho 2004]. The descriptive statistics and the results of Dunn's multiple comparisons test are shown in Tables 3 and 4.

Regarding PI, BOP and SAI variables, it can be highlighted that significant intragroup differences from the beginning to the end of the study can be found ($p < 0.05$), while no significant intergroup differences were denoted for each time frame ($p > 0.05$). Analysing SI, significant intragroup differences were found in Group 1 comparing each time frame with T3 ($p < 0.05$), while no intragroup differences were found for group 2($p>0.05$). Intergroup comparisons

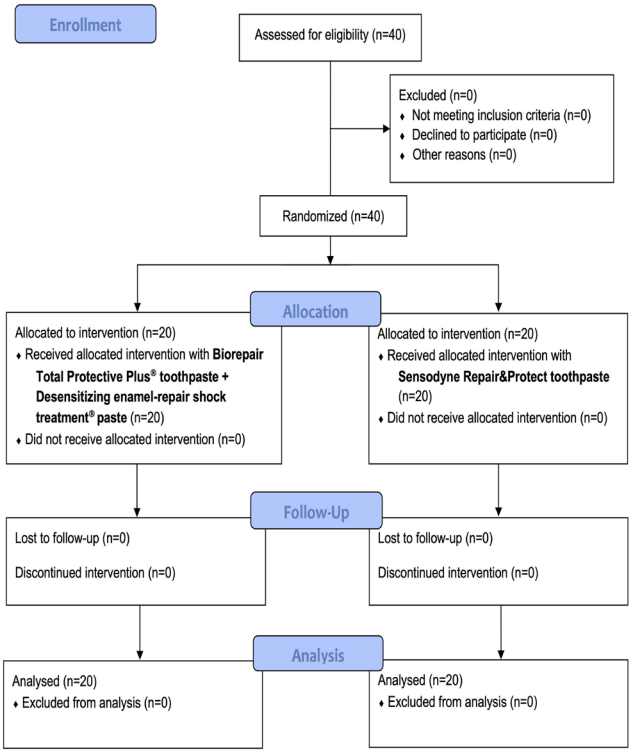

FIG. 1 Phases of the study according to CONSORT flow chart.

resulted not significant ($p > 0.05$). No significant intergroup and intragroup differences were detected ($p > 0.05$) regarding salivary pH, DMFT, and BEWE indices.

Discussion

It is well known that children are unable to perform proper oral hygiene at home, and several attempts have been made to facilitate the learning of oral hygiene manoeuvres and to motivate paediatric patients for routine visits [Uguz et al., 2023; Gurnani et al., 2023]. In addition to behavioural and cognitive interventions, the development of specific products for specific oral hygiene conditions is desirable. In this context, fluoride-free and low-fluoride toothpastes are currently being investigated [Latifi-Xhemajli et al., 2023]; the reason behind this choice is related to the fact that such toothpastes could avoid the side effects of higher fluoride intake [Patel et al., 2023]. In the last decade, toothpastes with biomimetic and remineralising activity have been developed and tested with promising results [Freda et al., 2016; Butera et al., 2023]. Therefore, preventive strategies including this type of approach should be pursued, because nowadays enamel demineralisations, including Molar-Incisor Hypomineralisation, are widespread in the paediatric population [Butera et al., 2021; Villani et al., 2023]. Given the above, the present work aimed to compare the efficacy of two remineralising treatments in paediatric patients with asthma and allergic rhinitis presenting enamel demineralisation, knowing that children suffering from these pathologies have worse oral health conditions [Vitale et al. 2023]. The null hypothesis of the study was partially accepted as no significant differences were detected between the two groups, but a significant change for some variables was shown over time. Notwithstanding, the effects of the proposed treatments

Group	β2	CS	AH	β2+CS	CS+AH	β2+CS+AH	β2+CS+MC	β2+CS+AH+MC
1	2(5.00)	1(2.50)	0(0.00)	7(17.50)	3(7.50)	6(15.00)	1(2.50)	0(0.00)
2	1(2.50)	2(5.00)	1(2.50)	9(22.50)	2(5.00)	4(10.00)	0(0.00)	1(2.50)
Total	3(7.50)	3(7.50)	1(2.50)	16(40.00)	5(12.50)	10(25.00)	1(2.50)	1(2.50)

Legend: β_2, beta-2 adrenergic agonists; CS, corticosteroids; AH, antihistamine drugs; MC, monoclonal antibodies.

TABLE 2 Number of patients (and percentage of total study sample in parentheses) grouped for therapeutic drugs.

were clinically relevant; in fact, both products led to an improvement in dental sensitivity and periodontal health, as SAI, PI and BoP showed significantly lower values after the 6-month study. Biomimetic hydroxyapatite was extensively tested by in vitro and clinical studies, and directly compared with fluoride, showing a non-inferior ability to prevent dental caries, no adverse effects, and a decreased dentinal hypersensitivity [O'Hagan-Wong et al., 2022]. Regarding calcium sodium phosphosilicate, instead, only dental sensitivity was investigated, and it seems to be effective only for periodontal patients, even though the remineralising activity can be applied also to the enamel surface [Zhu et al., 2015]. The periodontal treatment together with the oral hygiene instructions and the home use of the proposed toothpastes helped in decreasing PI and BoP from baseline. Regarding SAI, the fact that dental sensitivity was reduced could be due to the excipients of the toothpastes, specifically biomimetic hydroxyapatite for group 1 and calcium sodium phosphosilicate for group 2. Both compounds showed a marked remineralising activity by reducing dental sensitivity, with results that can be compared with previous studies [Ashwini et al., 2018; Butera et al., 2023 BIS]. Research on enamel remineralisation has led to the development of other compounds that are now commercially available, including amorphous calcium derivatives (casein phosphoprotein-amorphous calcium phosphate, or CPP-ACP) and beta-tricalcium phosphate, indicating that the topic is of great interest and that further studies are needed in this direction [Limeback et al., 2023; Desai et al., 2022]. Regarding DMFT, BEWE, and salivary pH variables, no significant changes during the study occurred; therefore, it can be assumed that the incidence of dental erosion and caries was not affected by the experimental treatments. Only for BEWE mean values a slight improvement was found, but with no significant difference among the time frames. Even though the study duration was 6 months, the follow-up period is probably too short to evaluate whether microbiological changes and erosion phenomena can be reduced. However, it should be considered that significantly higher DMFT scores were found only in asthmatic children aged 11-15 if compared to healthy controls according to a previous study [Botelho et al., 2011], and this situation could probably explain why in the present study no significant differences in DMFT were found, as the mean age of the study sample was 9.8 ± 2.4 years. The same can be found in other previous investigations, in which the mean age differs from the sample of the present study [Bairappan et al., 2020; Alaki et al., 2013]. Salivary pH, instead, depends on a delicate balance of different factors that can be easily modified by food and beverage intake [Pachori et al., 2018], so it is more likely that the twice-daily application of the toothpastes was not sufficient to cause a change in this index. Furthermore, it was demonstrated that asthma medication can worsen salivary pH [Widmer 2010], but this seems not to be confirmed in this study. Additionally, it seems that salivary flow rate (stimulated and not stimulated) is more affected than pH [Bairappan et al., 2020], therefore future studies should

Group	Time	SAI	BEWE	SI	DMFT
		Mean	Mean	Mean	Mean
		(SD)	(SD)	(SD)	(SD)
Zinc Hydroxyapatite	T0	1.95 (1.19) ^{a,b}	1.60 (0.75) ^{a}	2.35 (0.88) ^{a}	2.15 (2.48) ^{a}
	T1	1.4 (0.94) ^{a,b}	1.55 (0.76) ^{a}	2.00 (0.79) ^{a}	2.15 (2.48) ^{a}
	T2	0.70 (0.73) ^{c,d}	1.45 (0.60) ^{a}	1.72 (0.55) ^{a}	2.15 (2.48) ^{a}
	T3	0.25 (0.44) ^{d}	1.35 (0.49) ^{a}	1.30 (0.47) ^{b}	2.15 (2.48) ^{a}
Calcium sodium phosphosilicate	T0	1.65 (0.88) ^{a}	1.40 (0.75) ^{a}	1.85 (0.86) ^{a,b}	1.80 (1.24) ^{aC}
	T1	1.55 (0.83) ^{a,b}	1.35 (0.75) ^{a}	1.80 (0.89) ^{a,b}	1.80 (1.24) ^{a}
	T2	1.20 (0.77) ^{b,c}	1.35 (0.75) ^{a}	1.70 (0.86) ^{a,b}	1.80 (1.24) ^{a}
	T3	0.65 (0.67) ^{d}	1.30 (0.73) ^{a}	1.40 (0.94) ^{a,b}	1.80 (1.24) ^{a}

Legend: SAI, Schiff air index; BEWE, basic erosive wear examination; SI, susceptibility index.

TABLE 3 Descriptive statistics of the dental outcomes of the study. Same letters denote no significant intergroup and intragroup differences among the means ($p > 0.05$).

Group	Time	PI	BoP	Salivary pH
		Mean	Mean	Mean
		(SD)	(SD)	(SD)
Zinc Hydroxyapatite	T0	73.25 (22.79) [a]	51.30 (25.81) [a]	6.14 (1.09) [a]
	T1	52.65 (19.62) [b,c]	31.60 (25.27) [a,b,d]	6.43 (0.81) [a]
	T2	35.4 (20.04) [d,e]	22.90 (22.85) [d,e]	6.59 (0.39) [a]
	T3	15.41 (9.50) [f]	14.35 (21.48) [f,h]	6.84 (0.38) [a]
Calcium sodium phosphosilicate	T0	59.03 (32.38) [a,c,d]	32.19 (32.60) [a,b,e,f]	6.58 (0.75) [a]
	T1	35.47 (27.29) [b,e,g]	18.96 (25.80) [b,c,e,f]	6.69 (0.91) [a]
	T2	25.37 (25.67) [e,f,g]	15.63 (27.80) [c,d,h]	6.83 (0.6) [a]
	T3	12.54 (9.67) [f]	8.84 (20.34) [c,d,g,h]	6.89 (0.56) [a]

Legend: PI, plaque index; BoP, bleeding on probing.

TABLE 4 Descriptive statistics of the periodontal and salivary outcomes of the study. Same letters denote no significant intergroup and intragroup differences among the means ($p > 0.05$).

evaluate also the recording of this outcome. At last, the SI index was calculated to combine SAI, pH and BEWE scores to assess the patient's general susceptibility to tooth wear and salivary problems. However, in this study, only SAI was significantly affected by the experimental treatments, so the significant intragroup difference in SI at T3 in group 1 can only be attributed to the lower SAI at that time frame, suggesting that also for this index a longer follow-up study could be desirable. A limitation of the study is that a longer follow-up could probably help to reveal differences in dental erosion and caries incidence. Instead, it would be interesting to compare the products tested with other remineralising products, as mentioned above. Also, the quantity of toothpaste used could be increased, as no side effects are present for non-fluoride-based toothpastes. Other comparisons with ozonised water [Cosola et al., 2019] and low-level laser therapy [da Silva et al., 2022] could be performed. Future perspectives could include the evaluation of remineralising home treatment in conjunction with fissure sealants as a preventive strategy to improve the oral health of children with asthma and allergic rhinitis. Further studies could investigate the relationship between patients' dosages of anti-asthmatic and anti-allergic drugs with periodontal and hard tissue indexes, and evaluate the possible effects and interactions with the clinical use of remineralising products.

Conclusions

The 6-month remineralising treatments with both zinc hydroxyapatite and calcium sodium phosphosilicate resulted to be effective in reducing dental sensitivity and improving periodontal conditions assessed with BoP and PI in children suffering from asthma and allergic rhinitis, while no effects on salivary pH, tooth wear and caries incidence were found.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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