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The control of pain due to dentin hypersensitivity in individuals with molar–incisor hypomineralisation: a protocol for a randomised controlled clinical trial

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ABSTRACT

Introduction Dentin hypersensitivity (DH) is defined as high sensitivity of the vital dentin when exposed to thermal, chemical or tactile stimuli. Two mechanisms are required for the occurrence of DH: (1) the dentin must be exposed and (2) the dentinal tubules must be open and connected to the pulp. Molar–incisor hypomineralisation (MIH) is a qualitative abnormality of a genetic origin that affects tooth enamel and, in most cases, is accompanied by DH. The control of tooth sensitivity is fundamental to the successful treatment of MIH. The aim of the proposed randomised, controlled, clinical trial is to evaluate the effectiveness of different protocols for the control of DH in patients with teeth affected by MIH.

Methods and analysis One hundred and forty patients who meet the inclusion criteria will be allocated to four groups. Group 1 will be the control group (placebo). In Group 2, sensitive teeth will be sealed with PermaSeal (Ultradent). In Group 3, sensitive teeth will receive low-level laser (LLL, AsGaAl) at a wavelength of 780 nm (Laser XT Therapy, DMC, São Carlos, Brazil). In Group 4, sensitive teeth will be treated with both LLL and PermaSeal (Ultradent). DH will be evaluated 15 min after the application of the treatments and the patients will be reevaluated 1 week, 1 month, 3 months and 6 months after the treatments. The primary outcome of this study is change in pain/sensitivity, when evaluated through a Visual Analogue Scale, to determine the effectiveness of the proposed treatments, as well as differences among the evaluation times for each proposed treatment.

Ethics and dissemination This protocol has been ethically approved by the local medical ethical committee (protocol number: 4.020.261). Results will be submitted to international peer-reviewed journals and presented at international conferences.

Trial registration number NCT04407702.

Strengths and limitations of this study

► The randomised design will be used to compare different treatment protocols.
► The patients and the evaluator of the degree of sensitivity will be blinded to the allocation.
► We are comparing a more conventional treatment (sealant), with a more current therapy (low-level laser), bringing a sense of innovation to the study.
► Besides the evaluation of the treatment separately, the evaluation of their combined use is another strength.
► The researcher in charge of applying the products will not be blinded due to the different forms of clinical manipulation of the products, which is a limitation.

exposure of the dentinal tubules causes a reduction in the pain threshold, leading to a response from nerves in the pulp characterised by a rapid, acute, intense pain associated with the mechanoreceptor hydrodynamic mechanism. The proper diagnosis is essential to the establishment of adequate treatment.[1 2]

Brännström's hydrodynamic theory is the most widely accepted for explaining mechanisms that involve the triggering of pain sensations in DH. According to this theory, sensitivity is the result of the rapid movement of the fluid contained in the interior of the dentinal tubules. When a stimulus is applied to the dentin, the fluids within the tubules move both towards the pulp and in the opposite direction, producing a mechanical deformation of the nerve fibres found in the interior of the tubules or at the pulp/dentin interface, which is transmitted to the central

INTRODUCTION

Dentin hypersensitivity (DH) is defined as high sensitivity of vital dentin exposed to thermal, chemical or tactile stimuli. The

nervous system as a sensation of pain.[3] Two mechanisms are required for the occurrence of DH: (1) the dentin must be exposed and (2) the dentinal tubules must be open and connected to the pulp.[4]

Molar–incisor hypomineralisation (MIH) is a qualitative abnormality of genetic origin that affects tooth enamel. Clinically, MIH presents itself as yellowish-white or brownish demarcations larger than 1 mm that involve the permanent first molars and, occasionally, the incisors. This condition is generally accompanied by DH, frail enamel and high susceptibility to caries.[5]

Raposo *et al* investigated the prevalence of DH in molars affected by MIH and concluded that hypersensitivity was significantly greater on affected teeth than on unaffected teeth. The authors also found an association between mild-to-moderate cases and DH, which could not be proven for severe cases due to the high frequency of cavities.[6] The principal aim of the treatment of DH is to improve quality of life through the control of pain by suppressing nerve impulses or by the obliteration of the dentinal tubules.[7]

It is believed that the exacerbated sensitivity that the teeth affected by MIH may present can be explained by the high porosity of the affected area, which allows microorganisms to penetrate the enamel and reach the dentinal tubules, causing a subclinical inflammatory reaction of the pulp cells.[8 9]

There is not a defined protocol in the literature for the treatment of DH, but some alternatives have been proposed, such as fluoride varnishes, occlusal sealants, arginine/calcium carbonate products and casein phosphopeptide–amorphous calcium phosphate.[7 10–12] However, it is important to emphasise that we do not have enough evidence and, therefore, it cannot be said that one treatment is more effective than the other.[13]

Fragelli *et al* followed the adhesion resistance of resin sealants on first molars affected by MIH for 18 months and concluded that there was no significant difference in durability between affected and unaffected molars, what suggests that they may be a good option for treatment.[14]

Low-level laser (LLL) has been used as treatment for DH. In a literature review, Shintome *et al* concluded that both high-level laser and LLL are effective in the treatment of cervical DH. The reviewed studies also reported that treatment with laser offers greater patient comfort and enables longer lasting results in comparison to dentifrices and desensitising agents, as light acts directly on the dental tissue, promoting morphological changes in the dentin, stimulating the pulp tissue and making treatment more lasting.[15]

The control of tooth sensitivity is a fundamental factor to the successful treatment of MIH. Therefore, this paper proposes the evaluation of the effectiveness of different protocols for the control of DH.

METHODS
Overview
The aim of the proposed randomised, controlled, clinical trial is to evaluate the effectiveness of different protocols for the control of DH in patients with teeth affected by MIH. This protocol follows the Standard Protocol Items for Randomised Trials recommendations, as presented in table 1.

The study will be conducted in accordance with the ethical precepts stipulated in the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2008). The protocol was approved by the Ethics Committee (Certificate of Presentation for Ethical Appreciation number 31651120.7.0000.5509/ report number 4.020.261—Universidade Metropolitana

Table 1 Schedule of enrolment, interventions, and assessments of the study

| | Enrolment | Allocation | Study period | | | | | |
| | | | Post allocation | | | | | Close-out |
			0	t_1	t_2	t_3	t_4	t_5
Enrolment:								
Eligibility screen	x							
Informed consent	x							
Allocation		x						
Interventions:								
Control			x	x	x	x	x	x
Sealant			x	x	x	x	x	x
LLL			x	x	x	x	x	x
LLL and sealant			x	x	x	x	x	x
Assessments:								
Pain			x	x	x	x	x	x

0, baseline; LLL, low-level laser; t_1, immediately after treatment; t_2, 1 week after the treatment; t_3, 1 month after the treatment; t_4, 3 months after the treatment; t_5, 6 months after the treatment.

de Santos - UNIMES) and this protocol is registered at ClinicalTrials.gov and it was first posted on 25 May 2020 and last updated on 25 November 2020. Patients will be informed of the possible risks involved in the experiment, the confidentiality of the data and the existence of a placebo group. All information will be delineated in the statement of informed consent (resolution number 196 of the National Board of Health, Ministry of Health, Brazil, 3 October 1996) and the explanations in order to obtain this consent will be made by the same researcher that will apply the treatments. Two copies of the statement will be signed—one for the volunteer and one for the researchers. This consent form has been submitted as an online supplemental file. The statement will declare the commitment on the part of the researchers to provide adequate treatment for the participants in the placebo group at the end of the study and to the subjects of the other groups at the end of 6 months, if the pain symptoms have not improved. The offered treatment, in this case, will be that which achieved the best result in the initial 4 weeks of the study. The participants will be told that they may withdraw from the study at any time for any reason, if they so desire. The researchers will also be able to remove the participants from the study, if deemed necessary.

Participants

Patients between between 18 years and 35 years of age, selected at the Clinic of the School of Dentistry of UNIMES (Santos, Brazil), will participate in the study. Data collection will also take place in this same location. The sample size was determined based on the primary outcome of the study: final pain Visual Analogue Scale (VAS). Based on the data from,[16] our initial sample size estimation was of 24 subjects per group for a significant level of 0.05 and an estimated test power of 80%. To account for the possible non-parametric distribution of the data, 15% more subjects must be added to each group.[17] Another 25% will be added to account for possible dropouts, resulting in 35 subjects per group. G*Power V.3.1.9.6 was used to perform the calculations.

Patient and public involvement statement

Patients will not be involved in the conceptualisation of the study design, nor will they conduct it. After the analysis of the data, volunteers will be invited to a meeting and the results will be shared, in case they wish to attend it.

Experimental design

A randomised, double-blind (subject and evaluator of pain), parallel, interventional study will be conducted at the dental clinic of UNIMES. The study will be conducted following the Consolidated Standards of Reporting Trials guidelines (http://www.consort-statement.org/).[18] Pain will be evaluated using the VAS after stimulation with compressed air from the triple syringe and using an exploratory probe at the time of recruitment (baseline), immediately after treatment, as well as 1 week, 1 month,

3 months and 6 months after treatment. The study will follow the flowchart presented in figure 1.

Inclusion/exclusion criteria

During the first visit to the clinic, a form addressing the volunteer's medical history will be filled out. Each volunteer will then be submitted to a clinical examination for the determination of his/her oral status. Next, the inclusion and exclusion criteria will be applied to determine the eligibility of the volunteers.

Inclusion criteria

► Age between 18 years and 35 years
► Good overall health;
► At least one tooth with MIH and DH reported in the cervical region with sensitivity equal to or greater than 4 on the VAS.

Exclusion criteria

► Active caries or defective restorations on the tooth to be analysed.
► Sufficient dentin loss that requires restorative treatment or periodontal surgery.
► Having undergone any professional desensitising treatment in the previous 6 months.
► Having used a desensitising paste in the previous 3 months.
► Use of anti-inflammatory drugs or analgesics at the time of recruitment.
► Currently pregnant or nursing.

Recruitment

Recruitment will be made through announcements on the clinic (pictures and publications). An initial evaluation will be performed by a researcher who is trained to diagnosis MIH. After the volunteer reports the occurrence a tooth with hypersensitivity, the researcher will assess the sensitive tooth using cold air from the triple syringe (2 s of compressed air at a pressure of approximately 40 psi with the syringe perpendicular to the tooth surface at a distance of approximately 0.5 cm). Neighbouring teeth will be protected with cotton rolls or the examiner's fingers.[19] The volunteer will then indicate a whole number between 0 (the absence of pain) to 10 (worst pain possible) on the 10-cm VAS that best describes his/her perception of pain. The data will be stored in appropriate files with the identification of each patient. The possible decrease in sensitivity will, probably, increase adherence to the protocol.

Allocation and blinding

The participants will be randomly assigned to three experimental groups and a control group.

For the random distribution of volunteers, randomisation will be carried out by drawing lots using the website www.randomizer.org. Briefly, the mean of the initial VAS scores will be determined for each subject and the participants will be randomly allocated to the experimental groups ensuring similar initial VAS scores among the
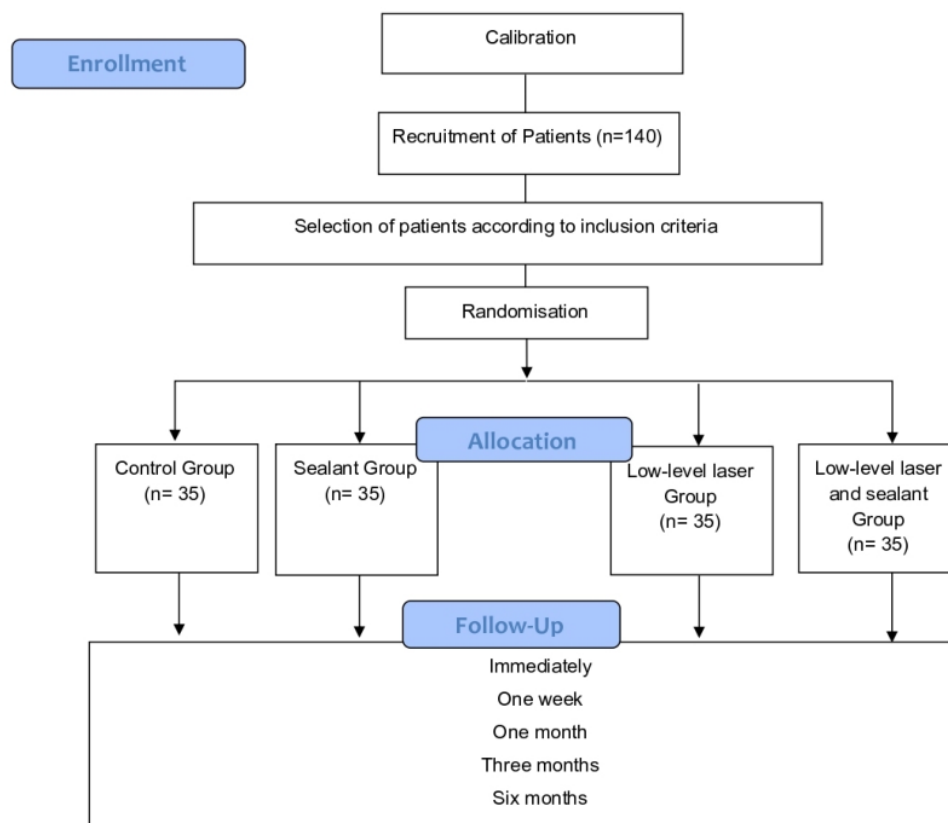
Figure 1 Activity flowchart in accordance with Consolidated Standards of Reporting Trials.

different treatments. All teeth with hypersensitivity in each volunteer will be evaluated using the VAS and the mean will be considered for the initial score. All teeth with hypersensitivity will be treated and reassessed using the VAS. The mean will then be calculated for the final sensitivity score.

Two weeks prior to the onset of the study, the volunteers will undergo a wash-out period, in which they will only use oral hygiene products donated by the researchers. These products will be used through to the end of the study. The oral hygiene kit will contain a soft-bristle toothbrush (Professional Lab Series, Colgate Palmolive), fluoride toothpaste with no desensitising agent (Elmex) and dental floss (Colgate). The participants will be extensively trained with regards to all of the procedures involved in the experiment.

All volunteers and the evaluator of the degree of sensitivity will be blinded to the allocation, they will not know to which group the participants belong. Unblinding in not permissible. The researcher in charge of applying the products will not be blinded due to the different forms of clinical manipulation of the products. A researcher who will not be involved in the application of treatments and has no conflicts of interest will be responsible for generating the allocation sequence and assigning patients to treatments.

Recruitment is intended to start on January 2021, the primary completion anticipated date is 30 August 2021

and the anticipated study completion date is 10 December 2021.

Procedures

The treatment sessions will be performed by a trained researcher following the manufacturer's instructions for each product and in accordance with scientific evidence regarding treatment with LLL. The neural desensitising protocol will involve the use of LLL (Therapy XT, DMC) and the obliteration protocol will involve the use of a resinous sealant (PermaSeal, Ultradent). The participants in the placebo group will use only the conventional oral hygiene kit during the 4 weeks of the study and will receive simulated treatment involving the application of a rubber cup with no product and sham irradiation with the laser device adjusted to 0 W. The participants will be allocated to four groups according to the proposed treatments. If, by request, participants decide to withdraw from the study, they will suffer no harm. However, improvement in sensitivity and its follow-ups should encourage patients to keep coming. Data from those who choose to discontinue will not be used for analysis. No adverse effects are expected from any of the treatments.

Control group

Group 1 will be the control group, which will receive no treatment. The volunteers in this group will receive the same instructions as the other groups and will undergo both treatments, except that water will be used instead of

the sealant and the laser device will be set to a power of 0 W. In other words, the same irradiation procedure will be performed but without the emission of light.

Sealant group

The volunteers in Group 2 will receive treatment with sealant (Permaseal, Ultradent), which is a photopolymerisable methacrylate-based resin. The teeth to be sealed will be isolated and 35% phosphoric acid will be applied for 20 s, followed by rinsing and drying the dental surfaces. A thin layer of PermaSeal will be applied to the tooth surface for 5 s and photopolymerised for 20 s. The occlusion will then be evaluated. The volunteers will return 1 week, 1 month, 3 months and 6 months after the final treatment session for reevaluation using the VAS.

Low-level laser group

The volunteers in Group three will receive irradiation with AsGaAl laser at a wavelength of 780 nm (Laser XT Therapy, DMC, São Carlos, Brazil) with relative isolation. A power metre (Laser Check, MMOptics, São Carlos, Brazil) will be used to determine the power of the equipment before and after all treatment interventions. The power will be set to 100 mW; energy density will be 35 J/cm^2 (considering a spot size of 0.028 cm^2 of the equipment) and the dose will be 1 J per point. Irradiation will be performed on a cervical point, an apical point and a point precisely over the lesion, totalling a dose of 3 J. Treatment will be performed in 3 sessions with a 72-hour interval between sessions.

During the laser treatments, both the volunteer and operator will use protective eyewear and all rules of safety will be obeyed. The volunteers will return 1 week, 1 month, 3 months and 6 months after the final treatment session for reevaluation using the VAS.

LLL and sealant group

The volunteers in Group 4 will receive the same irradiation administered to Group 3. During the last session, these volunteers will also receive the same sealant applied in Group 2. The volunteers will return 1 week, 1 month, 3 months and 6 months after the final treatment session for reevaluation using the VAS.

Data analysis and statistical evaluation

DH will be determined by a researcher who will be blinded to the treatments. This evaluation will be performed 15 min after the application of the treatments (Mehta *et al*, 2014) using the same method described above for the determination of the initial degree of sensitivity. The volunteers will be re-evaluated for the determination of sensitivity 1 week, 1 month, 3 months and 6 months after the treatments. These evaluations will be recorded on blank sheets of paper that will only indicate the number of the volunteer and the tooth evaluated.

The initial VAS score will be subtracted from the scores obtained 1 week and 4 weeks after treatment in all groups and the data will be submitted to statistical analysis. The change in sensitivity evaluated through VAS in the

different groups and periods is the primary outcome of the study, as it is the main objective of the treatments. Descriptive statistics will involve the calculation of mean and SD values. Inferential statistics will involve tests of normality and equal variance, which will determine the appropriate statistical tests. The level of significance will be set to 5%. The 3-month and 6-month data from the three experimental groups (not the placebo group) will be analysed in the same way.

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