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Associação de dois analgésicos não evita a sensibilidade causada pelo clareamento dental de consultório: ensaio clínico randomizado, triplo cego.

Cascavel - PR
2018

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Dissertação apresentada ao Programa de Pós-Graduação em Odontologia em cumprimento parcial aos requisitos para obtenção do título de Mestra em Odontologia, área de concentração Odontologia, linha de pesquisa Materiais Dentários Aplicados À Clínica Odontológica, APROVADO(A) pela seguinte banca examinadora:

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Ninguém vence sozinho, obrigada a todos!

EPÍGRAFE

“Conheça todas as teorias, domine todas as técnicas, mas ao tocar uma alma humana, seja apenas outra alma humana.”

Carl Jung

Associação de dois analgésicos não evita a sensibilidade causada pelo clareamento dental de consultório: ensaio clínico randomizado, triplo cego.

RESUMO

Introdução: A administração de drogas intra-orais isoladamente não foi capaz de reduzir a SD após o clareamento, o objetivo deste estudo foi determinar se associação de duas drogas pode induzir a analgesia a um nível mais elevado. **Metodologia:** Um ensaio clínico randomizado, paralelo, triplo-cego foi conduzido com 115 pacientes, os quais receberam uma associação de cetorolaco de trometamina 10mg e paracetamol 750mg ou placebo. A primeira dose administrada 1h antes do clareamento e as doses extras a cada 8h durante 48 h. A SD foi registrada nas escalas: VAS (0-10) e NRS (0-4) em diferentes períodos: durante o clareamento até 1h, 6h, 12h, 24h e 48h pós-clareamento. A cor foi registrada inicialmente e 1 mês após o clareamento, com as escalas visuais e um espectrofotômetro. O risco absoluto foi avaliado pelo teste Qui-quadrado. A intensidade de sensibilidade para ambas as escalas foi realizada pelo teste de ANOVA e Mann-Whitney. Comparações entre os tempos, dentro de cada grupo, foram realizadas pelo teste de Friedman. As alterações de cor entre os grupos foram comparadas pelo teste t de Student (α=0.05). **Resultados:** Não foram observadas diferenças estatisticamente significantes entre os grupos para o risco de SD e cor, porém intensidade da SD no grupo experimental diminuiu no período de 12 a 24h ($p > 0.04$) e 24 a 48 h ($p > 0.03$) após o clareamento ($p > 0.05$). **Conclusão:** A associação de paracetamol e toragesic não reduz a prevalência de SD, mas reduz a intensidade de SD após 12h do clareamento de consultório. **Relevância clínica:** O uso de dois analgésicos foi capaz de diminuir a intensidade de SD decorrente do clareamento de consultório após 12 horas do mesmo.

Palavras-chave: Sensibilidade da dentina, peróxido de hidrogênio, clareamento dental, analgésicos.

Combination of two analgesics does not avoid bleaching-induced tooth sensitivity: a randomized, triple-blind clinical trial.

ABSTRACT

Background: Administrating intraoral drugs alone was not able to reduce the TS after bleaching; the objective of this study was to determine if an association of two drugs could induce analgesia at a higher level. ***Methods****:* A triple-blind, parallel-randomized clinical trial was conducted with 115 patients receiving either an association of ketorolac tromethamine 10mg /acetaminophen 750mg or a placebo. The first dose was administered 1h before the in-office bleaching, and extra doses every 8h for 48h. The TS was recorded on VAS (0-10) and NRS (0-4) scales, during bleaching and1-6h, 12-18h, 18-24h, 24-48h post-bleaching. The color was measured before and one month after dental bleaching using two visual shade guide and spectrophotometer. The absolute risk of TS was evaluated by Chi-square test. The TS intensity for both scales were compared with ANOVA tests and Mann-Whitney U test. Comparisons between times within each group were performed by the Friedman test. The color changes between groups were compared by the Student t-test ($\alpha = 0.05$). ***Results****:* No significant differences in the absolute risk of TS and color between the groups ($p > 0.05$), however the intensity of TS decreased in the experimental group for the periods 12 to 24h ($p > 0.04$) and 24 to 48 h ($p > 0.03$). ***Conclusion:*** The ketorolac tromethamine/acetaminophen association prior to in-office bleaching does not reduce the risk, but reduce the intensity of TS after 12h. ***Practical Implications:*** Using two analgesics was capable to prevent TS arising from in-office dental bleaching after 12h.

Keywords**:** Dentin Sensitivity, Hydrogen Peroxide, Tooth Bleaching, Analgesics.

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LIST OF ABBREVIATIONS

ADA	American Dental Association
ASIC	Acid-sensitive ion channels
ATP	Adenosine triphosphate
CDC	Center for Disease Control and Prevention
cm	Centimeters
COX	Cyclooxygenase Enzyme
GPCR	G protein coupled receptors
HP	Hydrogen peroxide
h	Hours
K2P	Two-pore potassium
mg	Milligrams
NRS	Numeric Rating Scale
NSAID	Nonsteroidal anti-inflammatory drug
RTK	Receptor tyrosine kinases
SGU	Shade Guide Units
TRP	Transient Receptor Potential
TS	Tooth sensitivity
VAS	Visual Analogue Scale
ΔSGU	Variation Shade Guide Units
ΔE	Color Variation

LIST OF SYMBOLS

%	Porcentage
α	Alpha (level of significance)
®	Registered
Δ	Delta
δ	Delta
<	Smaller

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SUMMARY

1. ARTICLE

“Combination of two analgesics does not avoid bleaching-induced tooth sensitivity: a randomized, triple-blind clinical trial.”

INTRODUCTION

Due to its effectiveness and the increasing quest for whiter teeth by the general population, tooth bleaching has become a popular aesthetic dental procedure [1]. Currently, there are two main dentist-supervised techniques: the at-home or in-office bleaching. The at-home bleaching the patients are instructed to wear the bleaching tray daily, for periods ranging from 2 to 6 weeks, however, some patients do not want to use the trays [2]. In this clinical scenario, in-office bleaching has emerged more popular than home use because highly concentrated products may promote faster tooth whitening, without to wear the bleaching tray [3].

However, in-office bleaching using 35% hydrogen peroxide (HP) has a long history of tooth sensitivity (TS) [4,5] that is, in average, four times higher than that produced by at-home bleaching [6]. In recent clinical trials, authors reported an absolute risk of TS varying from 67% to 100% [6-9], which means that in the best condition, 6 patients in every 10 will experience pain during treatment. To the extent of the authors knowledge, the reasons of the bleaching-induced TS are not clear. The TS seems to result from the easy passage of the HP through the enamel and dentin to the pulp, causing pulp damage and a reversible inflammation process [1].

Since 2009, some authors have investigated the use of anti-inflammatory drugs for reduction of this adverse effect [6,10,11]. In their studies, the use of ibuprofen, a nonsteroidal anti-inflammatory, just reduced TS immediately up to 1 hour after bleaching [10,11]. The administration of other medicines such as a selective anti-inflammatory drug (etoricoxib 60 mg), a steroidal anti-inflammatory drug (dexamethasone 4 mg) or the combination of codeine and acetoaminophen (Tylex® 30 mg) was not capable of reducing this side effect [6,11].

The lack of efficacy of the intra-oral drugs tested in preventing bleaching-induced tooth sensitivity could be originated from an inflammatory response of the dental pulp through with the liberation of bradykinin [12] and substance P, which are involved in the process of inflammation and pulp pain [13,14].

The acetomynophen 750mg (not yet investigated alone in this dose), to acts by blocking impulse generation within the bradykinin-sensitive chemo-receptors and is also thought to have an analgesic effect by antagonizing of substance P in the spinal cord [3]. However, it is a nonsteroidal anti-inflammatory drug (NSAID), with very weak anti-inflammatory activity [15] and HYLLESTED et al., [16], suggests the addition of another

NSAIDs to paracetamol, may confer additional analgesic efficacy compared with paracetamol alone.

The ketorolac tromethamine may be indicated because it is a highly potent member of a new class of compounds having analgesic and anti-inflammatory activity, a single 10 mg tablet given orally to human volunteers following surgery provided pain relief equivalent to that provided by 10 mg of morphine given intramuscularly, whereas it was inactive in tests for narcotic activity [17].

Perhaps the use of two analgesics can induce analgesia a higher level that to use only one drug, to reduce the risk and intensity of bleaching-induced TS. Therefore, this parallel, triple-masked, randomized clinical trial aimed to evaluate the effect of an acetaminophen and ketorolac tromethamine, administered perioperatively for 48h, on the risk and intensity of bleaching-induced TS. The color change was also evaluated as secondary outcome.

MATERIAL AND METHODS

Ethics Approval

This clinical investigation was approved (protocol number 45733615.6.0000.0109) by the scientific review committee and by the Committee for the protection of human subjects of the University of Paraná – UNIPAR (Cascavel, PR, Brazil). This clinical report follows the protocol established by the Consolidated Standards of Reporting Trials statement [18] and followed the methodology used by DE PAULA et al.,[11] DE PAULA et al.,[8] REZENDE et al.,[6] and COPPLA et al.,[19].

Protocol registration

This clinical trial was registered in clinicaltrial.gov clinical registry under protocol # NCT03343392 and in the Brazilian clinical trials registry under the identification number REQ:5743 and can be assessed in the following link: http://www.ensaiosclinicos.gov.br.

Trial design, settings and locations of data collection

This was a randomized, parallel, placebo-controlled, triple-mask clinical trial, in which the patient, operator and evaluator were masked to the group assignment. A third researcher, not involved in the evaluation process, was responsible for the randomization process, and delivery and guidance on the administration of the drugs. This study was performed from 01/2016 to 12/2017 in the city of Cascavel (Paraná, Brazil). All bleaching procedures were carried out within the Clinics of the Dental School of the State University of Oeste do Paraná (Cascavel, Paraná, Brazil).

Recruitment

Each volunteer recruited for eligibility in the research, was registered in the form especially created for this study in the public domain statistical software Epi Info™ Center for Disease Control and Prevention (CDC) (Atlanta, Georgia, USA). Two weeks before the bleaching procedures, all the volunteers, who were patients who searched treatment in the clinics of the dental schools, received a dental prophylaxis with pumice and water in a rubber cup and signed an informed consent form.

Eligibility criteria

Patients included in this clinical trial were at least 18 years old and had good general and oral health, and did not report any type of TS. The participants were required to have six caries-free maxillary anterior teeth and without restorations, absence of periodontal disease and must reviewed and signed the informed consent form. The central incisors should be shade A2 or darker as judged by comparison with a value-oriented shade guide (Vita Classical, Vita Zahnfabrik, Bad Säckingen, Germany).

Two calibrated investigators in each Dental School independently performed the color evaluation with a value-oriented shade guide. The two examiners, masked to the allocation assignment, scheduled these patients for bleaching and evaluated their teeth against the shade guide at baseline and 1 month after the procedure. The two examiners were required to have an agreement of at least 85% (Kappa statistic) before beginning the study evaluation.

Participants with anterior restorations or dental prosthesis, with orthodontics apparatus, with severe internal tooth discoloration (tetracycline stains, fluorosis, pulpless teeth) were not included in the study. Additionally, pregnant/lactating women, participants with any other pathology that could cause sensitivity (such as recession, dentine exposure, presence of visible cracks in teeth), taking anti-inflammatory and/or analgesic drugs, bruxists or participants that had undergone tooth-whitening procedures were also excluded.

Patients that reported some earlier or present health problems in stomach, heart, kidney and liver, participants reporting continuous use of anti-inflammatory and/or analgesic drugs were excluded. Additionally, diabetics, hypertensive or patients with known allergy to acetaminophen/codeine and lactose were excluded from the study.

Sample size calculation

The primary outcome of this study was the absolute risk of TS. The absolute risk of TS was reported to be approximately 86% [11,20] for the bleaching product Whiteness HP Maxx (FGM, Prod. Odont. Ltda, Joinville, SC, Brazil). Thus, a minimum sample size of 114 patients was required to have a 90% chance of detecting, as significant at the two-sided 5% level, a decrease in the primary outcome measure from 87% in the control group to 60% in the experimental group (which represent a difference of 31% in the absolute risk of TS).

Random sequence generation and allocation concealment

We used blocked randomization (block sizes of 2 and 4) with an equal allocation ratio. The randomization process was performed by software freely available on the internet

(www.sealedenvelope.com). Opaque and sealed envelopes containing the identification of the groups were prepared by third party, not involved in the study intervention. This third researcher, not involved in the evaluation process, was responsible for the randomization process, delivery and guidance on the administration of the drugs. A single random sequence was performed.

Study intervention

Patients were divided into acetaminophen/ketorolac tromethamine and placebo groups. All patients received the same bleaching treatment, which was performed by five operators in the Dental School. One hour before in-office bleaching patients received either the acetaminophen 750 mg (Paracetamol 750 mg, Bioativa compounding pharmacy, Cascavel, PR, Brasil) and ketorolac tromethamine oral 10 mg (Toragesic® 10 mg, EMS Sigma Farma, Hortolândia, SP, Brasil) or placebo, for both medicines in identical tablets or capsules. The operator administered the first dose of drug 1h before the protocol, and extra doses were administered every 8h for 48h to keep a safe maximum daily dosage of 4000 mg of acetaminophen and 40 mg of ketorolac tromethamine [21].

The tablets of Toragesic® and Paracetamol were removed them from their original packaging and inserted them whole into new vials made especially for this research. We stored the capsules in individual vials containing 6 capsules of Paracetamol and 6 capsules of Toragesic® required for each bleaching session. The placebo tablets for Paracetamol contained starch lactose free (Bioativa compounding pharmacy, Cascavel, PR, Brasil) and the placebo capsules for Toragesic® contained base past, lactose free (Oro-tab®, Bioativa compounding pharmacy, Cascavel, PR, Brasil).

One hour before starting the bleaching application, the masked researcher responsible for drug administration gave the first dose to the patient. Then, they isolated the gingival tissue of the teeth to be bleached using a light-cured resin dam (Top Dam, FGM Dental Products, Joinvile, SC, Brasil), and each tooth was light-cured for 10s (Radii-cal, SDI, Victoria, Australia). After placement of a lip retractor (Arcflex, FGM, Joinvile, SC, Brasil), the researcher used the 35% hydrogen peroxide gel (Whiteness HP Automixx, FGM, Joinvile, SC, Brasil) in a single 50-minute application for both groups in accordance with the manufacturer's directions. Two bleaching sessions were performed with 1 week apart. All participants were instructed to brush their teeth regularly using fluoridated toothpaste.

Tooth sensitivity (TS) evaluation.

The TS was evaluated during bleaching up to 1h, from 6h up to 12h, from 12h up to 24h, from 24h up to 48h post-bleaching in both sessions. The patient was asked to indicate the numerical value of the degree of sensitivity for each one of the periods above, using a five-point Numeric Rating Scale (NRS) where 0 = none, 1 = mild, 2 = moderate, 3 = considerable and 4 = severe [8,11,20,22-24].

Additionally, the participants were also instructed to record the pain intensity using the Visual Analogue Scale (VAS) [25,26]. This scale is a 10-cm horizontal line with scores of 0 and 10 at their ends, where 0 = no sensitivity and 10 = severe sensitivity. The patient should mark with a vertical line across the horizontal line of the scale the intensity of the TS. Then, the distance in mm from the zero ends was measured with the aid of a millimeter ruler.

Firstly, the data of TS from both bleaching sessions were merged. For this purpose, the worst score (NRS scale) and numerical value (VAS scale) obtained in both bleaching sessions at each assessment period was considered for statistical purposes and determination of the overall risk and intensity of TS.

If the patient scored zero (no sensitivity) in all time assessments from both bleaching sessions, this patient was considered to be insensitive to the bleaching protocol. In all other circumstances, the patients were considered to have sensitivity to the bleaching procedure. This dichotomization allowed us to calculate the absolute risk of TS, which represented the percentage of patients that reported TS at least once during treatment. We also calculated the overall TS intensity.

Color evaluation.

Color evaluation was recorded before and one month after dental bleaching. Color evaluation was never performed immediately after each bleaching session so that the effect of dehydration and demineralization on color measures could be avoided. The measurement area of interest for shade matching was the middle one third of the facial surface of the anterior central incisor, according to the American Dental Association (ADA) guidelines [5,20,27].

The color evaluation was performed with the value-oriented shade guide Vita Classical (Vita Zahnfabrik) and the Vita Bleachedguide 3D-MASTER (Vita Zahnfabrik). Additionally, an objective color evaluation was performed with the spectrophotometer Vita Easyshade (Vita Zahnfabrik).

For the subjective examination, with shade guide Vita Classical (Vita Zahnfabrik), the shade guide's 16 tabs were arranged from highest (B1) to lowest (C4) value. Although this scale is not linear in the truest sense, we treated the changes as representing a continuous and

approximately linear ranking for the purpose of analysis, as already performed in several published studies [11,22,23,25-28]. The Vita Bleachedguide 3D-MASTER (Vita Zahnfabrik) contains lighter shade tabs and is already organized from highest (0M1) to lowest (5M3) value [28,29].

The two examiners, masked to the allocation assignment, scheduled these patients for bleaching and evaluated their teeth against the shade guide at the different time assessments. Color changes were calculated from the beginning of the active phase through to the individual recall times by calculating the change in the number of shade guide units (ΔSGU), which occurred toward the lighter end of the value-oriented list of shade tabs. In the event of disagreements between the examiners during shade evaluation, a consensus was reached.

For the objective examination, before the spectrophotometer measurement, an impression of the maxillary arch was taken with dense silicone paste (Zetaplus and Oranwash® Kit, Zhermack, Italy). The impression was extended to the maxillary canine and served as a standard color measurement guide for the spectrophotometer. For each dental component to be evaluated, a window was created on the labial surface of the molded silicone guide using a metal device with a radius of 3 mm and well-formed borders [23].

The shade was determined using the parameters of the Easyshade device where it indicated the following values: L*, (a*) and (b*), in which L* represents the value from 0 (black) to 100 (white) and a* and b* represent the shade, where a* is the measurement along the red-green axis and b* is the measurement along the yellow-blue axis. The color comparison before and after treatment is given by differences between the two colors (ΔE), which is calculated using the formula: $\Delta E = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$ [30,31].

Blinding

This was a triple-mask study, in which the patient, operator and evaluator were blinded to the group assignment.

Statistical analysis

The analysis followed the intention-to-treat protocol and involved all participants who were randomly assigned [18]. In case of missing data, the last observation was carried forward. The statistician was also blinded to the study groups. The absolute risk of TS of both groups was compared using the *Chi-square test* (α=0.05).

The comparison of the TS intensity obtained with the VAS and NRS scales of the two groups at the two different assessment points was performed with two-way repeated measures

ANOVA and ANOVA test for pairwise comparison to variances homogeneous and to variances are not homogeneous was performed using the Mann-Whitney U test. Comparisons between times within each group were performed using the Friedman test. The color changes between groups (ΔSGU and ΔE between baseline vs. one-month post-bleaching) were compared using a Student t-test. In all statistical tests, the significance level was 5%. We performed all analyses by using the software Epi Info™ WebSite version 7.2.2.2 (Center for Disease Control and Prevention (CDC) (Atlanta, Georgia, USA).

RESULTS

Baseline data and characteristics of included participants

A total of 204 participants were examined in a dental chair to check if they meet the inclusion and exclusion criteria (Figure 1). In-office bleaching was performed in 115 patients out of these 89 examined participants. Baseline demographic and clinical characteristics were similar among the two groups (Table 1).

Adherence to the protocol and drop-outs

In the placebo group one patient was pregnant and the bleaching treatment was not realize and another patient discontinued intervention in this clinical investigation after the first bleaching session due to intense pain, this patient performed only one session. Five participants not attended the recall visits one-month post-bleaching, including the participant from the placebo group that discontinued treatment. For this participant, the last observation was carried forward for statistical purposes to keep the intention-to-treat analysis [18]. Figure 1 depicts the participant flow diagram in the different phases of the study design.

Risk and Intensity of bleaching-induced Tooth sensitivity

In regard to the absolute risk of TS, no significant difference was observed between groups as seen in Table 2 ($p = 0.414$). The tooth sensitivity intensity was less intense for Acetaminophen/ ketorolac tromethamine than the placebo group only during 12 to 24h and 24 to 48h (Table 2).

Collected datas of Tooth sensitivity

Four patients from the placebo group took an analgesic (rescue medication) to alleviate the bleaching-induced TS (Ibuprofeno 400 mg (Uniprofen, União Química Farm Nacional S/A, Embu-Guaçu, SP, Brasil). One patient from the acetaminophen/ ketorolac tromethamine group presented nausea after the second bleaching session due to intense pain. The data of these patients were included in the data analysis, following the intention-to-treat protocol. One participants in the Acetaminophen/ ketorolac tromethamine and in placebo group experienced pain after 48h.

Color evaluation

Significant whitening was observed in both study groups under the subjective and objective evaluation methods ($p < 0.05$). At the end of the bleaching protocol, a whitening of approximately 4 shade guide units was detected for both groups and the ΔE varied by approximately 7.0 units (Table 2). The results of the subjective (Vita Classical and Vita Bleachedguide) and the objective evaluation with the spectrophotometer matched the hypothesis of equality between the groups after bleaching. All participants observed color change, three volunteers got dissatisfied with the in-office bleaching treatment and one of them would not repeat and neither indicate the bleaching, one participant would not repeat the bleaching and another one would not indicate the in-office bleaching for another people.

Adverse effects

One patient from the acetaminophen/ketorolac tromethamine group presented nausea, vomiting and malaise after the first bleaching session, but the patient finished the bleaching protocol.

DISCUSSION

Though tooth whitening is one of the most sought after procedures in dental offices, dental sensitivity remains the most common adverse effect reported by patients, often leading to discontinuation of treatment [24,32]. Nevertheless, this study demonstrated that approximately 78% of patients in both groups reported TS at some stage of bleaching, confirming the high prevalence of TS shown by previous studies [7,11,26,33].

The pain caused by mechanical, thermal and chemical stimuli result in release of various pro-nociceptive mediators (ATP, glutamate, kinins, cytokines), that activate sensory structures called nociceptors [34,35], present in the primary afferent neurons (Aδ and C nerve fibers), to enhance nociceptive signal transmission to the central nervous system, so-called "peripheral sensitization" [36].

Thus, tissue damage is often accompanied by the accumulation of endogenous factors (referred as inflammatory soup), released from activated nociceptors or from non-neural cells that reside within or infiltrate into the injured area (as mast cells, basophils, platelets, macrophages, neutrophils, endothelial cells, keratinocytes and fibroblasts) [37]. This soup is represented for a wide array of signaling molecules, including neuropeptides (substance P), aracdonic acid metabolites (prostaglandins, thromboxanes, leukotrienes and lipoxins), bradykinin, vasoactive amines (histamine and serotonin), cytokines and chemokines [37] which have a recognized role in triggering and potentiating the nociceptive impulses [13,38]. Furthermore, nociceptors express one or more cell surface receptors, as the G protein coupled receptors (GPCR), the TRP channels, the acid-sensitive ion channels (ASIC), the two-pore potassium channels (K2P), and the receptor tyrosine kinases (RTK), that are capable of recognizing and responding to each of these pro-inflammatory or pro-algesic agents [39].

Unquestionably, the most common approach to reducing nociception process and inflammatory pain involves inhibiting the synthesis or accumulation of components of the inflammatory soup [37] or to acting on any of the channels cited above. Therefore a single drug not always is able to avoid pain or avoid the bleaching-induced TS, as demonstraded in the clinical trials that administered nonsteroidal anti-inflammatory drugs [10,33] selective anti-inflammatory drugs [11], corticosteroids [6] and even codeine.

A second approach, as the used in this research, is the administration of two drugs of different analgesic classes, acting at different points of the pathophysiological mechanisms involved in pain [16]. However, the two drugs used (Ketorolac Tromethamine to work through the inhibition of cyclooxygenase (COX), regulatory effect at the opioid receptors and in the nitric oxide synthase [40], and, Paracetamol to work through the inhibition of

bradykinin and by antagonizing of substance P [3] were not capable to reduce the absolute risk of TS experienced by these patients.

By the present research, what could justify the inefficacy of the medicines administered per-oral rout to avoid the bleaching-induced TS, is that several factors (the immune system, lymphatic drainage, urinary excretion and morphological characteristics of the dentin substrate) may modulate the amount of drug that reaches the plasma and extracellular fluid in the pulp chamber [8], and this amount is not able to control the pro-nociceptive mediators that enhance excitability of the nerve fiber. So far, this could explain the minimization of the bleaching-induced TS, when desensitizing agents were applied topically [7,20,26].

However, it is worth mentioning, that the intensity of tooth sensitivity in the Ketorolac Tromethamine/Acetaminophen group was lower after 12h postbleaching in the present investigation. This result can be explain, because the nociceptors transmit their input centrally via two different types of axons as, the rapidly conducting thinly myelinated Aδ fiber and the more slowly conducting unmyelinated C fiber axons. The initial pain sensed in the first phase, is extremely sharp, is associated with the fast-conducting Aδ fibers and the drugs administered in this study were not capable prevent sensitization of this kind of fiber by the pro-nociceptive mediators, causing TS during up to 12h after tooth bleaching. After 12h, with development of the moderate inflammatory process [41], the pain sensed in the second phase typically more prolonged, less intense and mediated by C fiber axons [42], may have been reduced by the drugs used in this research, in case, the Paracetamol that is antagonizing of substance P [3] which is released mainly by C fiber [38].

In a literature review, HAYWOOD [4] reported that tooth sensitivity from bleaching usually affects the smaller teeth, such as the maxillary lateral incisors and the mandibular incisors. The present clinical study found the most painful tooth during and imediataly post bleaching are the mandibular incisors, but not the maxillary lateral incisors. COSTA et al., [1] and others in a histological pulp evaluation after bleaching, showed notable damage to the pulp tissue of mandibular incisors but not premolars. In this research, the premolars were the tooth less cited by patients. The less sensitivity in the premolars can be explained because about 87% of all axons that enter human premolars are nonmyelinated C fibers, with lower intensity pain [43].

It is important to note the mandibular canine (43) was also very cited by patients, HENRY et al [44] indicated the regulation of innervation density is a dynamic process, and the number of nerve fibers can vary depending on the developmental stage, type of tooth and

in the presence of following orthodontal procedures. Maybe the the TS bleaching-induced is more related with quantity and type of tooth inervation that the size of teeth.

Our study used 3 methods for color evaluation. Although the spectrophotometer provides an objective color assessment, previous studies reported that shade guides showed more accurate visual correlation and allowed more accurate monitoring, and consistent and reliable color of teeth [28]. VITA Classical is frequently used in dental bleaching studies [29,45,46], however, it has a nonlinear color arrangement, as it was not primarily designed for evaluation of dental bleaching. This was the reason we also used the shade guide VITA Bleachedguide 3D-MASTER.

According to the Vita Classical shade guide, the degree of whitening observed in this study, for both groups, was approximately 5 SGU. Although comparison with other studies are quite difficult due to different bleaching products and protocols [45], studies that performed two in-office bleaching sessions with 35% hydrogen peroxide yielded similar results [5,20,47,48].

The Bleachedguide VITA 3D-MASTER shade guide was developed for evaluation of color changes in bleaching studies; it presents more uniform color distribution compared to Vita Classical [28] and it is already organized from low-to-high value. It has the disadvantage of being rarely employed [6,45,49,50], preventing authors from comparing these results with the literature. In face of that, the authors of this study discourage the sole use of this tool.

Regardless of the instrument used for color measurement, they were all convergent in the findings that groups were statistically similar, which means that the perioperative use of the tromethamine/acetaminophen association did not jeopardize the whitening efficacy of the bleaching procedures. Intra-oral use of different drugs has been used to prevent bleaching-induced TS, but based on the present study and on the findings from earlier studies we reached the overall conclusion that the use of intra-oral drugs did not affect the whitening efficacy [6,10,33].

CONCLUSION

The use of ketorolac tromethamine/acetaminophen association prior to in-office bleaching does not reduce the risk, but capable to decrease the intensity of TS arising from in-office dental bleaching after 12h post bleaching treatment.

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ANEXX

Table 1: Baseline Characteristics of the participants

Table 1: Baseline Characteristics of the Participants.			
Characteristic		**Acetaminophen/ ketorolac tromethamine (n=58)**	**Placebo (n=57)**
Baseline color (SGU; mean ± SD)		6.2 ± 1.5	6.1 ± 1.8
Age (years; mean ± SD)		22.3 ± 3.5	23.0 ± 4.3
Gender (female; %)		63.8	65.0
Race	White (%)	91.4	89.5
	Black (%)	0	0
	Mulatto (%)	8.6	8.8
	Yellow (%)	0	1.7
Smoker		0	2
Patients used bright toothpaste		0	0

Table 2: Primary and secondary outcome in the intention-to-treat population

Table 2. Primary and Secondary Outcome in the Intention-to-Treat Population.*			
	Acetaminophen/ ketorolac tromethamine N=58	**Placebo N=57**	***P***
Primary outcome			
Comparison of the number of patients who experienced TS during the bleaching regimen			
TS (%)	42 (72,41)	45 (78,95)	0,414*
Secondary outcome			
Comparison of TS intensity experienced by patients from the treatment groups at different assessment points using NRS pain scale (ε).			
During bleaching	1 (0-2) A	1 (0-2) A	0,60**
Medians and interquartile range during Up to 1 h	1 (0-3) B	2 (0-3) B	0,28**
Medians and interquartile range during 1h to 6 h	1 (0-2) C	2 (0-3) C	0,18**
Medians and interquartile range during 6h to 12 h	1 (0-2) D	1 (0-2) D	0,07**
Medians and interquartile range during 12 to 24 h	0 (0-1) E	1 (0-1) E	0,04ϕ
Medians and interquartile range during 24 to 48 h	0 (0-0) F	0 (0-1) F	0,03ϕ
Comparison of TS intensity experienced by patients from the treatment groups at different assessment points using VAS pain scale (ε).			
During bleaching	1.0 (0-4) A	1.0 (0-4) A	0,77**
Medians and interquartile range during Up to 1 h	2.5 (0-5) B	3.5 (0-6) B	0,20**
Medians and interquartile range during 1h to 6 h	2.8 (0-5) C	4.0 (0-6.5) C	0,06**
Medians and interquartile range during 6h to 12 h	1 (0-3) D	2 (0-5) D	0,17**
Medians and interquartile range during 12 to 24 h	0 (0-1) E	1 (0-3) E	0,03ϕ
Medians and interquartile range during 24 to 48 h	0 (0-0) F	0 (0-1) F	0,03ϕ
Means and standard deviations of ΔSGU obtained with the Vita Classical and Vita Bleachedguide and ΔE obtained by spectrophotometer between baseline vs. 1-month post bleaching along (***).			
Color evaluation tool Vita Classical	4.7 ± 1.6	4.6 ± 1.9	0.83
Color evaluation tool Vita Bleached	7.1 ± 3.3	6.3 ± 2.8	0.18
Color evaluation tool ΔE	7.0 ± 3.4	7.1 ± 4.0	0.83
Comparision of Participants who Experienced Tooth Sensitivity Imediataly Postbleaching on the Maxillary and Mandibular Anterior Teeth			
Maxillary Anterior Teeth	1	3	
Mandibular Anterior Teeth	15	12	
Maxillary and Mandibular Anterior Teeth	15	15	
Kind of teeth with sensitivity symptoms more and less cited for the participants.			
41	17	11	
31	17	9	
42	13	12	

43	10	13
32	12	10
24	3	2
14	4	2
34	4	4
44	4	5
21	3	6

** Chi-square test (p = 0,414).*

****ANOVA test for comparison of groups within each assessment time to variances homogeneous.**

ϕ Mann-Whitney test for comparison of groups within each assessment time to variances not homogeneous.

ε Within each column, significant differences are represented distinct uppercase letters (Friedman test)

***** Paired t-test**

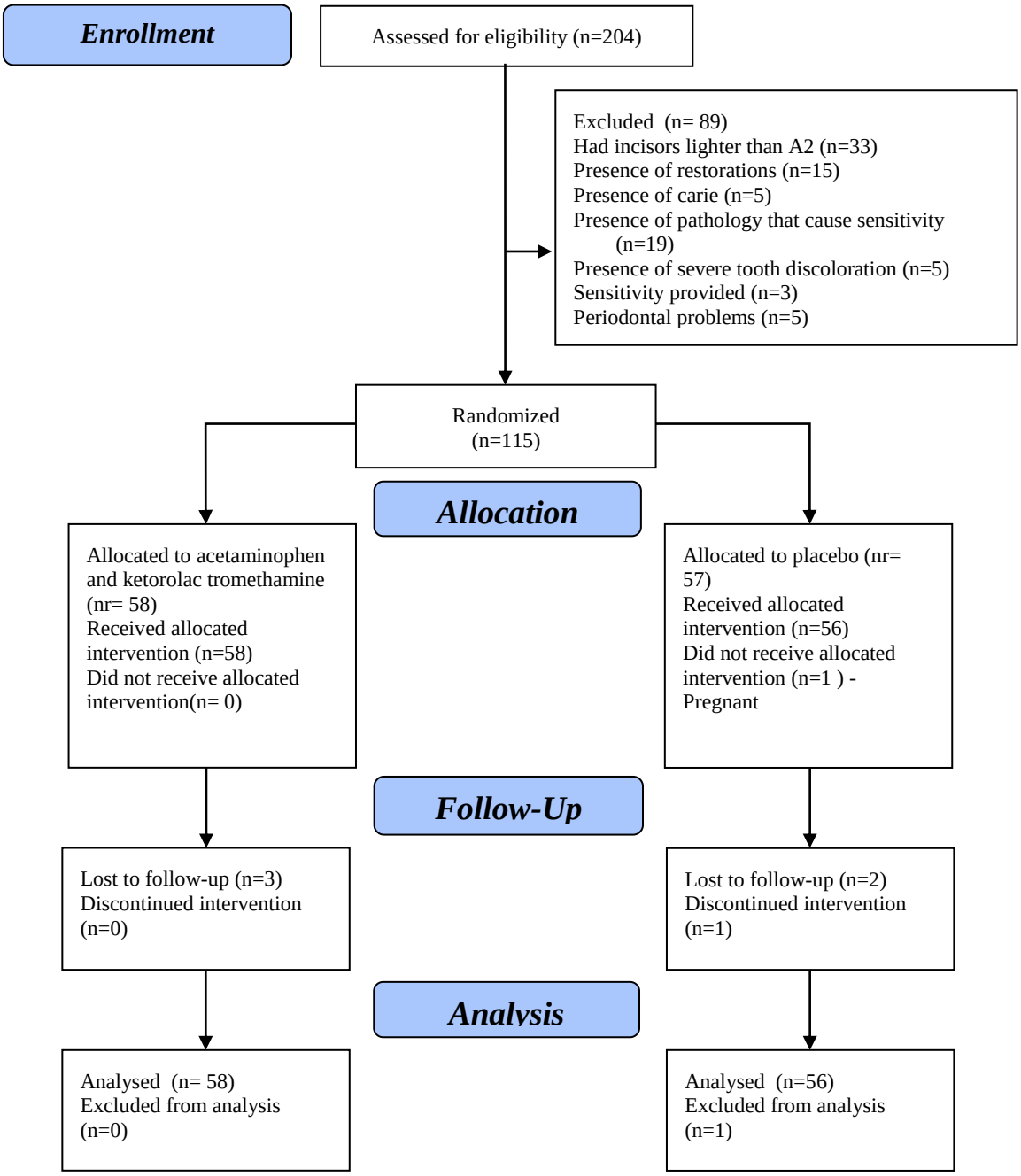

Figure 1 - Flow diagram of the clinical trial including detailed information on the exclused participants.

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PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: O efeito de diferentes medicamentos na prevenção da sensibilidade causada pelo clareamento dental.

Pesquisador: Eloisa Andrade de Paula

Área Temática:

Versão: 5

CAAE: 45733615.6.0000.0109

Instituição Proponente: ASSOCIACAO PARANAENSE DE ENSINO E CULTURA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.596.016

Apresentação do Projeto:

O presente estudo objetiva determinar o efeito de diferentes medicamentos (tópicos e sistêmicos) na redução da sensibilidade dental causada pelo clareamento de consultório de dentes vitais utilizando peróxido de hidrogênio 35%, bem como verificar a efetividade da alteração de cor. O projeto de pesquisa é apresentado no modelo 'guarda-chuva ou universal', contend 5 projetos; para cada projeto serão selecionados no mínimo 60 pacientes para cada grupo experimental e 60 pacientes para o grupo placebo, totalizando 600 pacientes no projeto universal. As mudanças de cor serão avaliadas utilizando espectrofotômetro (Easy Shade) e escala Vita organizada por ordem de valor. Duas escalas destinadas a avaliar a intensidade de dor (escala verbal de 5 pontos e EVA escala visual analógica) serão utilizadas para avaliar o nível de sensibilidade imediatamente, 1 hora, 24 e 48 horas após o tratamento de clareamento de consultório.

Objetivo da Pesquisa:

Objetivo Primário:

Determinar o efeito de diferentes medicamentos (Tópicos e Sistêmicos) na redução da sensibilidade dental causada pelo clareamento de consultório de dentes vitais, utilizando peróxido de hidrogênio 35%.

Objetivo Secundário:

Endereço: Praça Mascarenhas de Moraes, 8482
Bairro: Umuarama **CEP:** 87.502-210
UF: PR **Município:** UMUARAMA
Telefone: (44)3621-2849 **Fax:** (44)9127-7860 **E-mail:** cepeh@unipar.br

• Avaliar o efeito do medicamento tópico gel de nitrato de potássio 5% + fluoreto de sódio 0.2% (Dessesibilize KF 0.2% - FGM) aplicado sobre os dentes 10 dias antes, durante e 48 horas após o tratamento, no risco absoluto de sensibilidade decorrente da realização da técnica de clareamento dental em consultório;
• Avaliar o efeito do dentifrício tópico Colgate Sensitive Pró-Alívio (Colgate) com ação dessensibilizante aplicado sobre os dentes 10 dias antes, durante e 48 horas após o tratamento, no risco absoluto de sensibilidade decorrente da realização da técnica de clareamento dental em consultório;
• Avaliar o efeito do anti-inflamatório não seletivo para as isoformas COX (Toragesic SL 10 mg), administrado de 8 em 8 horas, durante 48 horas, no risco absoluto de sensibilidade decorrente da realização da técnica de clareamento dental em consultório;
• Avaliar o efeito do anti-inflamatório não seletivo para as isoformas COX (Toragesic SL 10 mg) combinado ao medicamento analgésico (paracetamol 750 mg), administrado de 8 em 8 horas, durante 48 horas, no risco absoluto de sensibilidade decorrente da realização da técnica de clareamento dental em consultório;
• Avaliar o efeito do antioxidante (vitamina E ephynal 400 mg), administrado de 8 em 8 horas, durante 48 horas, no risco absoluto de sensibilidade decorrente da realização da técnica de clareamento dental em consultório.
• Em cada projeto será avaliado a alteração de cor causada pelo agente clareador.

Avaliação dos Riscos e Benefícios:

Riscos:

A utilização do peróxido de hidrogênio pode ocasionar efeitos adversos como sensibilidade dentinária. Devido o poder de penetração dos agentes
clareadores no interior do dente,pode causar inflamação da polpa dentária.Efeito adverso com o uso do medicamento (alteração gástrica ou
cardíaca).O contato direto do agente clareador com o tecido gengival pode ocasionar ardência, descamação e ulceração, portanto, para evitar tal
ocorrência, será utilizada uma barreira de proteção fotopolimerizável (Top Dam – FGM).

Benefícios:

Os pacientes voluntários receberão de maneira gratuita todo o tratamento de clareamento dental, proporcionando uma melhor estética para os seus dentes.

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Comentários e Considerações sobre a Pesquisa:

Prezada Pesquisadora,

Agradecemos as alterações realizadas.

A pesquisa se apresenta de forma conclusiva e pode ser executada, uma vez que os pesquisadores contemplaram todos os requisitos éticos para a sua realização.

Considerações sobre os Termos de apresentação obrigatória:

TCLE - Este documento contém as informações para o bom entendimento e anuência dos participantes da pesquisa, devendo ser elaborado em duas vias, sendo uma retida pelo sujeito da pesquisa e a outra arquivada pelo pesquisador.

DECLARAÇÃO DE PERMISSÃO DE UTILIZAÇÃO DE DADOS ¿ Este documento se apresenta de forma satisfatória com a autorização pelo responsável do local (Instituição) onde a pesquisa será realizada.

Recomendações:

Salientamos que os procedimentos devem assegurar a confidencialidade, a privacidade, a proteção da imagem e a não estigmatização, garantindo a não utilização das informações em prejuízo das pessoas e/ou comunidade, inclusive em termos de autoestima, de prestígio econômico e/ou financeiro.

Conclusões ou Pendências e Lista de Inadequações:

Prezado pesquisador, vosso projeto foi aprovado sem restrições.

De acordo com o Conselho Nacional de Saúde, Resolução 466/2012:

O termo de consentimento livre esclarecido deve ser elaborado em duas vias, sendo uma retida pelo sujeito da pesquisa, ou por seu representante legal, e uma arquivada pelo pesquisador.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_512724.pdf	08/06/2016 15:23:23		Aceito
Folha de Rosto	folhaderosto.pdf	08/06/2016 15:23:02	Gabriela Ulian de Oliveira Somensi	Aceito

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UNIVERSIDADE PARANAENSE - UNIPAR

Continuação do Parecer: 1.596.016

Projeto Detalhado / Brochura Investigador	projeto.doc	08/06/2016 12:40:15	Eloisa Andrade de Paula	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEviavoluntario.docx	08/06/2016 12:39:44	Eloisa Andrade de Paula	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEviapesquisador.docx	08/06/2016 12:37:59	Eloisa Andrade de Paula	Aceito
Cronograma	Cronograma.docx	15/04/2016 16:40:21	Eloisa Andrade de Paula	Aceito
Outros	FormColetaDadosEVA.pdf	23/02/2016 17:33:42	Fabiana Scarparo Naufel	Aceito
Declaração de Instituição e Infraestrutura	UnioesteCampoEstudo.pdf	23/02/2016 17:31:59	Fabiana Scarparo Naufel	Aceito
Declaração de Instituição e Infraestrutura	UniparCampoEstudo.pdf	23/02/2016 17:31:46	Fabiana Scarparo Naufel	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

UMUARAMA, 16 de Junho de 2016

Assinado por:
Nelton Anderson Bespalez Corrêa
(Coordenador)

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COMITÊ DE ÉTICA EM PESQUISA ENVOLVENDO
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TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

1 Título da Pesquisa: ***O efeito de diferentes medicamentos na prevenção da sensibilidade causada pelo clareamento dental.***

2. Pesquisadores: Profa. Dra. Eloisa Andrade de Paula; Profa. Dra. Alessandra Naufel, Profa Dra. Vera Lúcia Schmitt, Profa. Dra. Gabriela Ullian, acadêmica Yara Grubert Pedrão, acadêmica Tainara Conte, Acadêmica Mayara Buratti, acadêmica Mariana Macedo Ribas, acadêmica Letícia Oliveira Santos, acadêmica Monique Dandara Martins Costa.

3. Proposição: determinar o efeito de diferentes medicamentos (Tópicos e Sistêmicos) na redução da sensibilidade dental causada pelo clareamento de consultório de dentes vitais utilizando peróxido de hidrogênio 35% e verificar a efetividade da alteração de cor causada por esse produto.

4. Procedimentos do Experimento: Esta técnica de clareamento é realizada no consultório odontológico onde o cirurgião-dentista aplica o produto clareador sobre os dentes com vitalidade pulpar. Para proteção da gengiva será utilizado uma barreira gengival (Top Dam, FGM) que garante que apenas os dentes selecionados entrarão em contato com o gel clareador. Todo este procedimento leva aproximadamente 1 hora, e serão realizadas 2 sessões com intervalo de 1 semana entre elas. Alguns pacientes durante o clareamento apresentam sensibilidade dos dentes, esta é ocasionada pela ação do produto. No caso de ocorrer sensibilidade severa serão feitas aplicações de dessensibilizante o paciente medicado com ibuprofeno 600 mg.

5. ***Local da pesquisa*****:** O tratamento e exame clínico serão realizados na Clínica Odontológica do Curso de Odontologia da Universidade Estadual do Oeste do Paraná. Durante este período os voluntários serão acompanhados pelos pesquisadores para a verificação de qualquer efeito adverso.

6. Resultados esperados: A resposta da pesquisa pode trazer benefício clínico, pois se espera que a administração prévia dos medicamentos reduza ou previna a sensibilidade pós-operatória decorrente da realização da técnica de clareamento dental de consultório.

7. Análise crítica dos riscos e benefícios*:* A utilização de qualquer agente químico utilizado para o clareamento dental pode ocasionar efeitos adversos como sensibilidade, ardência, descamação e ulceração das mucosas bucais, dependendo da sensibilidade individual. Após o relato de qualquer efeito adverso (exceto sensibilidade), o tratamento com o clareador será imediatamente suspenso, com a retirada do sujeito da pesquisa. Quanto aos benefícios, os indivíduos da pesquisa terão seus dentes clareados, e receberão gratuitamente o clareamento, bem como o

agente utilizado para o tratamento de uma eventual sensibilidade. Os pacientes podem reclamar de algumas reações adversas dos medicamentos como tontura, inchaço das pernas e/ou pés, fraqueza e cansaço, pressão alta, enjôos, azia, desconforto no estômago e dor de cabeça, diarréia ou prisão de ventre, náuseas ou vômitos, úlcera de estômago ou duodeno que provocam eliminação de sangue vivo, ou fezes como borra de café, zumbido no ouvido ou tontura, inchaço das pernas, reações alérgicas tipo urticária e coceira. Serão dadas todas as informações sobre qualquer tipo de problema, formas de tratamento, encaminhamento e acompanhamento do adequado tratamento na clínica de pós-graduação da UNIOESTE ou na clínica da UNIPAR juntamente com a professora Gabriela Ulian.

8. Forma de acompanhamento e assistência e garantia de esclarecimentos: Os indivíduos terão a garantia de que receberão esclarecimento a qualquer dúvida, acerca dos procedimentos, riscos, benefícios e outros assuntos relacionados com a pesquisa. Os pesquisadores responsáveis assumem o compromisso de proporcionar informação atualizada obtida durante o estudo, ainda que esta possa afetar a vontade do indivíduo em continuar participando dele.

9. Retirada do consentimento: Os sujeitos têm a liberdade de se recusar a participar da pesquisa ou de retirar seu consentimento a qualquer momento, sem sofrer qualquer tipo de prejuízo, ou represálias de qualquer natureza.

10. Garantia de sigilo: Os pesquisadores se comprometem a resguardar todas as informações individuais, tratando-as com impessoalidade e não revelando a identidade do sujeito que as originou.

11. Formas de ressarcimento de despesas e de indenização: Os indivíduos não deverão terão qualquer despesa. Para o tratamento de efeitos adversos os custos estão previstos no orçamento do projeto.

12. Consentimento pós-informação

Eu, _____, certifico que tendo lido as informações acima e suficientemente esclarecido de todos os itens, pelos pesquisadores clínicos responsáveis: Eloisa Andrade de Paula, Alessandra Naufel, Vera Lúcia Schmitt, Gabriela Ullian, Yara Grubert Pedrão, Tainara Conte, Mayara Buratti, Mariana Macedo Ribas, Letícia Oliveira Santos, Monique Dandara Martins Costa. Estou plenamente de acordo com a realização do experimento. Assim, eu concordo em participar como voluntário do trabalho de pesquisa, exposto acima.

Certifico também ter recebido uma cópia deste Termo de Consentimento Livre e Esclarecido.

Cascavel, _____ de _____ de 20___.

ATENÇÃO: A sua participação em qualquer tipo de pesquisa é voluntária. Em caso de dúvida quanto aos seus direitos, entre em contato com a Comissão de Ética em Pesquisa Envolvendo Seres Humanos da UNIPAR. Endereço - Praça Mascarenhas de Moraes s/n -Centro, Umuarama/PR - 87.502-21 Telefone: 44-36242828 / 44-36212828 e-mail: cepeh@unipar.br ou com os pesquisadores Eloisa Andrade de Paula (42) 9989-9999 e Fabiana Scarparo Naufel (45) 9978-1515