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ORIGINAL ARTICLE

Perioperative use of an anti-inflammatory drug on tooth sensitivity caused by in-office bleaching: a randomized, triple-blind clinical trial

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Abstract
Objectives The aim of this study was to determine the effect of etoricoxib 60 mg on tooth sensitivity (TS) caused by in-office bleaching.
Materials and methods A triple-blind, parallel design, randomized clinical trial was conducted on 30 healthy, young adults who received either a placebo or etoricoxib. The drugs were administered 1 h before the bleaching process and after 24 h. Treatment was performed with 35 % hydrogen peroxide gel. The TS was recorded on three scales: VAS, 0–4, and 0–100. Shade evaluations were performed before and 30 days after bleaching with a visual shade guide and a spectrophotometer. The percentage of patients who reported TS at least once during treatment and the TS intensity were evaluated by Fisher's exact and Mann–Whitney *U* tests, respectively. Tooth color changes were evaluated by repeated measures ANOVA.
Results There were no significant differences in the percentage of patients with TS, intensity of TS, and color between the groups.
Conclusions and clinical significance The anti-inflammatory medication etoricoxib 60 mg was unable to reduce the presence and intensity of TS. NCT01300780 (protocol No. 17838/2010).

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Introduction

Vital tooth bleaching with a peroxide gel is generally recognized as a safe and effective procedure [1] and can be performed either using the at-home and in-office bleaching protocol [2]. Even though the at-home bleaching system is the most frequently recommended treatment for vital teeth, some patients do not want to use a bleaching tray or do not want to wait 2 to 3 weeks to see the results of the treatment [3]. Thus, another bleaching option is the in-office bleaching procedure. The effectiveness of this bleaching procedure is well established in the literature with an overall color change of 5 to 8 shade guide units (SGU) after two in-office bleaching sessions [2–9].

However, with the in-office procedure using 35 % hydrogen peroxide, there is a long history of tooth sensitivity (TS) and gingival irritation [10, 11]. Incidence levels of TS have been reported to be as high as 87 % [3, 5, 6], and this has been considered the main reason why patients have not successfully completed their whitening treatment [3, 8]. For instance, Schulte et al. [12] reported that of 28 subjects submitted to at-home bleaching, 4 discontinued the bleaching protocol because of TS.

As reported by Markowitz [13], many authors claim that bleaching-related pain is the result of the hydrodynamic theory of dentin sensitivity [14, 15]. However, although pain in bleached teeth can be evoked by thermal or other stimuli, as in dentin hypersensitivity, most patients complain of tingling or shooting pain (zingers) [15] without provoking stimuli. Moreover, pain after bleaching can affect intact

teeth without exposed dentin, which is in sharp contrast to dentin sensitivity when pain occurs in teeth with exposed dentin [13]. Based on this, it is suggested that TS resulting from bleaching may be due to the easy passage of the peroxide through the enamel and dentin and the production of pulp inflammation [16].

The observation that certain bleaching procedures increase pulpal expression of substance-P (a nerve-released vasoactive peptide) suggests that neurogenic inflammation may play a role in the onset of this side effect [17]; however, this should be further investigated. In addition to substance-P, arachidonic acid metabolites, such as prostaglandins (PGs), have a recognized role in triggering and subsequently potentiating nociceptive impulses that are transmitted to the central nervous system for the perception of pain [18]. The generation of PGs, which have been known to play a critical role in the pathogenesis of pulpal disease involves the cyclooxygenase (COX) pathway. There are at least two variants of COX: the COX-1, which is involved in physiological functions, and inducible COX-2, which is believed to be involved in the inflammatory response [19] and has been considered responsible for the production of PGs mediating inflammation and pain in inflamed pulps [20].

There are a number of materials and techniques for reducing TS that arises from bleaching [21]. The use of desensitizing agents, such as fluorides and potassium nitrate before or after at-home [22, 23] and in-office bleaching therapies [3, 5] or their inclusion in the bleaching formulations [22, 24] has been shown to be capable of reducing the experience of TS during bleaching treatment.

Another approach recently investigated was the preoperative use of ibuprofen [25]. Although this clinical alternative seems to be promising, the preoperative use of a single dose of ibuprofen 600 mg before the in-office bleaching protocol was shown to reduce TS only during but not after the treatment period. Ibuprofen is a nonsteroidal anti-inflammatory drug, which is believed to work through the inhibition of both constitutive COX-1 and inducible COX-2 [19].

Perhaps the use of a more selective anti-inflammatory drug, capable of inhibiting only the inducible COX-2 enzyme may be more effective in preventing the TS caused by the inflammatory response produced by in-office bleaching. In addition, the drug posology of the selected anti-inflammatory drug is more patient friendly since it requires taking the medicine once every 24 h. To the extent of the authors' knowledge, no study has so far addressed the use of a selective anti-inflammatory drug on TS. Therefore the aim of the present investigation was to determine the effect of etoricoxib 60 mg on TS caused by in-office bleaching. In the present study, we tested the hypothesis that the preventive use of a selective COX-2 anti-inflammatory drug would not affect the absolute risk of TS.

Materials and methods

This clinical investigation was approved (protocol No. 17836/2010) by the scientific review committee and by the committee for the protection of human subjects of the local university. The experimental design was in accordance with the CONSORT statement [26]. Based on pre-established criteria, 30 volunteers from the city of Guarapuava, Paraná, Brazil were selected for this study. Two weeks before the bleaching procedures, all the volunteers underwent dental screening and dental prophylaxis with pumice and water in a rubber cup and signed a term of free and informed consent.

Study design This was a randomized, triple-blind, placebo-controlled, parallel-group clinical trial, with an equal allocation rate to receive either one of two treatments. The study took place in the clinic of the Brazilian Association of Dentistry in Guarapuava, Paraná from August 2010 to December 2010.

Inclusion and exclusion criteria Patients included in this clinical trial were at least 18 years old and had good general and oral health. Participants were recruited by means of radio and TV advertisement. A total of 247 participants were examined in a dental chair to check whether they met the inclusion and exclusion criteria (Fig. 1). The participants were required to have six caries-free maxillary anterior teeth, without restorations on the labial surfaces. The central incisors had to be shade C2 or darker as judged by comparison with a value-oriented shade guide (Vita Lumin, Vita Zahnfabrik, Bad Säckingen, Germany). Participants who had undergone tooth-whitening procedures, presented anterior restorations, were pregnant/lactating, had severe internal tooth discoloration (tetracycline stains, fluorosis, and pulpless teeth), were taking any type of medicine, had bruxism habits, or any other pathology that could cause sensitivity (such as recession and dentin exposure) were excluded from the study, since they would not be immediately eligible for a cosmetic treatment, such as bleaching. Participants who reported some earlier or present health problems in the stomach, heart, kidney and liver, or participants continuously using any with anti-inflammatory and antioxidant action 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 % [3] for the bleaching product Whiteness HP Maxx (FGM, Joinville, SC, Brazil). Thus, 30 patients were required to have an 80 % chance of detecting, as significant at the two-sided 5 % level, a decrease in the primary outcome measure from 86 % in the control group to 41 % in the experimental group.

Study intervention Participants were randomly stratified by sex into the placebo and etoricoxib groups. The randomization

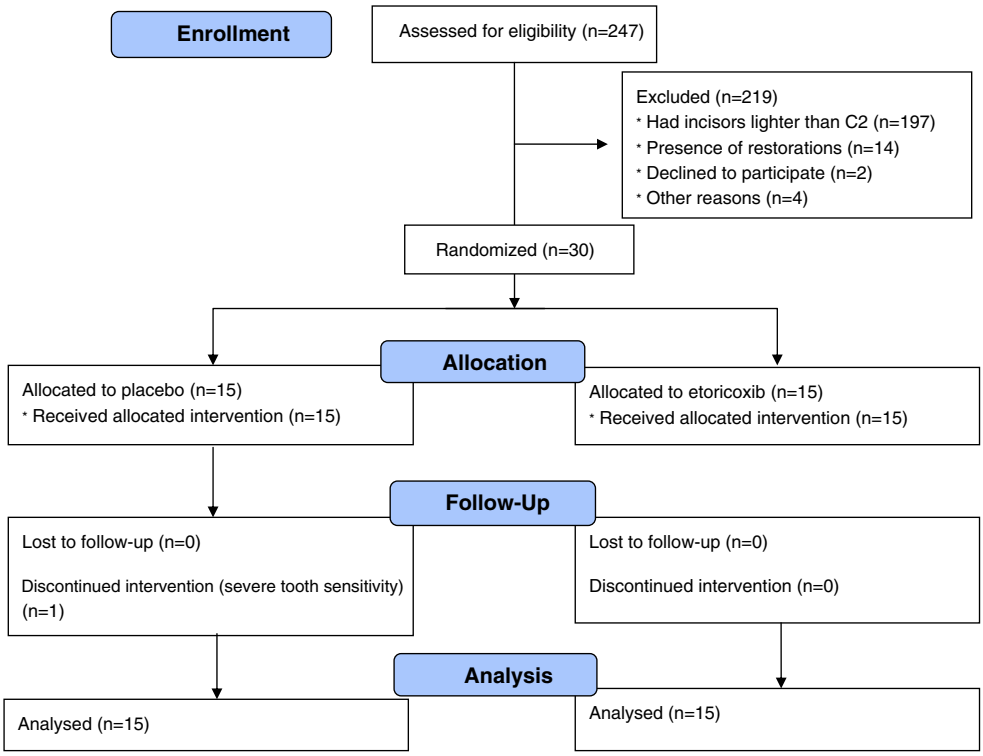

Fig. 1 Flow diagram of the clinical trial including detailed information on the excluded participants

process was performed by computer-generated tables by a third person not involved in the research protocol. Details of the allocated groups were recorded on cards contained in sequentially numbered, opaque, sealed envelopes. These were prepared by a third person not involved in any of the phases of the clinical trial. Once the participant was eligible for the procedure, and completed all baseline assessments, the allocation assignment was revealed by this envelope being opened by the mentioned third person. Neither the participant nor the operator knew the group allocation, both being blinded to the protocol.

The participants from the placebo group received a placebo (Talco pharma SM-200-Henrifarma produtos químicos e farmacêuticos LTDA, São Paulo, SP, Brazil) and participants from the etoricoxib group received a dose of a selective COX-2 inhibitor etoricoxib 60 mg (Arcoxia, MSD, Campinas, SP, Brazil). All the participants were watched to ensure that they took the drugs or placebo 1 h before treatment. The drugs were similar in appearance. A second dose of placebo or etoricoxib (60 mg) was administered 24 h after the first dose. At the time the participants were required to take the second dose of the medicine, the research auxiliary called him/her and asked him/her to take the medicine. This procedure was implemented to increase adherence to the protocol.

The gingival tissue of the teeth to be bleached was isolated using a light-polymerized resin dam (Top Dam, FGM, Joinville, SC, Brazil). The 35 % hydrogen peroxide gel (Whiteness HP Maxx, FGM) was used in three 15-min applications for both groups in accordance with the manufacturer's directions. The in-office bleaching agent was refreshed every 15 min during the 45-min application period. Two bleaching sessions with 1 week interval between them were performed. All participants were instructed to brush their teeth regularly using fluoridated toothpaste (Sorriso Fresh, Colgate-Palmolive, São Paulo, SP, Brazil).

Shade evaluation Shade evaluation was recorded before and 30 days after the bleaching treatment using two methods: subjective evaluation using a shade guide (Vita Lumin, Vita Zahnfabrik, Bad Säckingen, Germany) and an objective evaluation using the spectrophotometer (Easyshade, Vident, Brea, CA).

For the subjective examination, the 16 shade guide tabs were arranged from highest (B1) to lowest (C4) value, so that the color C2 was set at No. 7. Although this scale is not linear in the truest sense, the changes were treated as though they represented a continuous and approximately linear ranking for the purpose of analysis [5, 6, 11]. The measurement area of interest for shade matching was the middle one third of the facial surface of the anterior central incisor [11]. For calibration purposes, five patients who were not included in the sample because they were used in the pilot study, participated in the training phase of this study. The two examiners, blinded to the allocation assignment, scheduled these patients for bleaching and evaluated their teeth against the shade guide at baseline and 30 days after the procedure. The two examiners were required to have an agreement of at least 85 % (Kappa statistic) before beginning the study evaluation.

For the objective evaluation, a preliminary impression of the maxillary arch was made using dense silicone Adsil (Vigodent S/A Indústria e Comércio, Rio de Janeiro, RJ, Brazil). The impression was extended to the maxillary canine and served as a standard color measurement guide for the spectrophotometer. A window was created on the labial surface of the molded silicone guide for the central incisor to be evaluated. The window was made using a metal device with well-formed borders, with a radius of 3 mm [11]. Only one operator took all the measurements in all 30 patients, using Vita Easyshade (Easyshade, Vident, Brea, CA) before and 30 days after the bleaching therapy. The shade was determined using the parameters of the Easyshade device where the following values were indicated: 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 the difference between the two colors (ΔE), which is calculated using the formula: $\Delta E=((\Delta L^*)2+(\Delta a^*)2+(\Delta b^*)\ 2)1/2$ [11].

TS evaluation The patients recorded their perception of TS during the first and second bleaching sessions using three pain scales. A 5-point verbal rating scale (0=none, 1=mild, 2=moderate, 3=considerable, and 4=severe] [3, 5], a 0 to 100 numerical rating scale [27] and a visual analogue scale [25–29] using a 10-cm horizontal line with words "no pain" at one end and "worst pain" at the opposite end were used in this study. Subjects were asked to record whether they experienced TS during the treatment up to 1 h after, from 1 to 24 h and from 24 to 48 h after bleaching. The worst scores/numerical values obtained in both bleaching sessions were considered for statistical purposes. The values were arranged into two categories: percentage of patients that reported TS at least once during treatment (absolute risk of TS) and overall TS intensity.

Statistical analysis The analysis was performed after the intention-to-treat protocol and involved all participants who were randomly assigned [26]. The statistician was blinded to the study groups. The agreement between the examiners' objective evaluation was evaluated using the kappa statistic. The primary outcome absolute risk of TS was compared by using the Fisher's exact test at a 5 % level of significance. The relative risk as well as the confidence interval for the effect size was calculated.

TS intensity (secondary outcome) was also statistically analyzed. The mean/median and standard deviation/interquartile range of the three pain scales were calculated. Color change, another secondary endpoint, was used to assess the efficacy of the bleaching treatment. For subjective evaluation, the means and standard deviations of SGU at baseline and 30 days after bleaching for each group were calculated. In order to evaluate whether the bleaching therapies were effective or not, the data from SGU of both groups were submitted to a two-way repeated measures ANOVA. A post-hoc analysis (Tukey's test) was used to make pairwise comparisons. The ΔL, Δa, Δb, and ΔE values were evaluated by Student's t test.

The data sets were plotted on histograms and inspected for normal distributions. Some data did not appear to be normally distributed, and therefore, nonparametric statistical tests were used to compare the various treatments. Statistical analyses of three pain scales comparing the two groups at the three different assessment points were performed using the Mann–Whitney U test. Comparisons between times within each group were performed using the Friedman tests. In all statistical tests, the significance level was set at $\alpha=0.05$. p values less than or equal to 5 % indicated significant differences.

Table 1 Comparison of the number of patients who experienced tooth sensitivity during the bleaching regimen in both groups along with absolute and relative risks

Treatment	Tooth sensitivity (number of participants)		Absolute risk (95 % CI)	Relative risk (95 % CI)
	Yes	No		
Placebo	9	6	60 (35–80)	1.2 (0.73–2.0)
Etoricoxib	11	4	73 (48–89)	

Fisher's test ($p=0.69$)

Results

The mean age (years) of the participants in this study was similar between the groups (placebo, 26.4±6.8 and etoricoxib, 26.7±6.1). Fifty three and sixty percent of the participants from the placebo and etoricoxib groups were men. Figure 1

Table 2 Comparison of the number of patients (in percent) who experienced tooth sensitivity at the different assessment points for the two treatment groups

	Placebo	Etoricoxib
Up to 1 h	8 (53) Aa	9 (60) Aa
1 to 24 h	9 (60) Ab	11 (73) Ab
24 to 48 h	0 (0) Bc	2 (13) Bc

Within columns, similar uppercase letters indicate similar percentages. Within rows, similar lowercase letters indicate similar percentages (Chi-square test, $\alpha=0.05$)

Table 3 Comparison of tooth sensitivity intensity experienced by patients from the treatment groups at different assessment points using three pain scales

	0–4[a]		0–10[b]		0–100[b]	
	Placebo	Etoricoxib	Placebo	Etoricoxib	Placebo	Etoricoxib
Up to 1 h	2 (0/4) a, A	1 (0/3) a, A	3.3±2.9 a, A	2.6±2.4 a, A	40.1±28.7 a, A	37.3±26.7 a, A
1 to 24 h	1 (0/4) a, A	1 (0/3) a, A	2.4±2.7 a, A	2.2±2.8 a, A	30.6±28.6 a, A	22.5±29.3 a, A
24 to 48 h	0 (0/0) b, B	0 (0/1) b, B	0±0 b, B	0.1±0.4 b, B	0±0 b, B	1.6±4.5 b, B

Comparisons are valid only within the same pain scale. At each period, the two treatments were compared with Mann–Whitney *U* test and differences are represented by different lowercase letters. For each treatment, the three periods were compared with the Friedman test (α=0.05) and differences are represented by different uppercase letters

[a] Median (minimum/maximum) values

[b] Means and standard deviations

depicts the participant flow diagram in the different phases of the study design.

Tooth sensitivity

The data from 30 patients were used in this study after the intention-to-treat analysis. One patient from the placebo group received an analgesic after the second bleaching session due to considerable TS. In regard to the absolute risk of TS (primary outcome), no significant difference was observed between groups, as shown in Table 1 (p=0.69). The relative risk together with the 95 % confidence interval also shows evidence that the use of the experimental drug had no effect on the reduction of TS.

Table 2 depicts the number of participants who experienced TS during 48 h after bleaching. Most of the TS complaints occurred within the first 24 h (p<0.001), and only one of the participants experienced pain after 24 h. In regard to TS intensity (Table 3), the groups did not differ statistically according to the three pain scales used in this study (p>0.05).

Color evaluation

Significant whitening was observed in both study groups by means of the subjective and objective evaluation methods (p< 0.001). Whitening of approximately 4 to 5 SGU was detected for both groups (Table 4) and the ΔE varied from 7.2 to 8.1 (Table 4). The results of the subjective (visual shade guide) and the objective evaluation (spectrophotometer) matched the hypothesis of equality between the values after bleaching (p≈0.6 for both methods).

Discussion

Three pain scales were used to investigate the intensity of TS in this study, in order to allow comparison with previous literature studies that used different pain scales. The results of the present study show that the scales provided similar ratings, which is in agreement with previous literature findings on this topic [27]. Although this was not the main focus of the present investigation, it could also be observed that the experience of TS for most of the participants occurred within the first 24 h after bleaching, adding further evidence to the fact that this TS is transient.

As mentioned in the introduction, tooth whitening has been shown to produce a moderate inflammation process in the pulp, with visible changes in odontoblastic layer [30], however, contrary to our previous expectation the use of a selective anti-inflammatory drug (etoricoxib 60 mg) in a preventive approach was incapable of reducing TS arising from bleaching. One could attribute this to a possible lack of COX-2 expression in the pulp of bleached teeth soon after the bleaching procedure. Although an earlier study [20]

Table 4 Means and standard deviations of shade guide units (Vita Classical shade guide) and ΔL, Δa, Δb and ΔE (spectrophotometer) at different assessment points for the two treatment groups

	Placebo	Etoricoxib
Subjective evaluation—visual shade guide		
Time assessment		
Baseline	9.3±2.0 A	8.3±1.4 A
30 days after bleaching	3.9±1.8 B	4.5±1.6 B
Objective evaluation—spectrophotometer		
CIELab parameter		
ΔL	1.2±2.2 A	2.3±1.8 A
Δa	−0.73±1.0 B	−0.99±1.2 B
Δb	−6.7±2.3 C	−7.3±3.4 C
ΔE	7.2±2.5 D	8.1±3.3 D

Means indicated by the same uppercase letters indicate statistically similar means (two-way ANOVA, α=0.05). Comparisons are only valid within rows. Similar upper case letters indicate statistically similar means (Student's *t* test, α=0.05)

identified the presence of COX-2 expressing cells in inflamed human pulps by the immunohistological method, the inflamed pulp was obtained from carious teeth, and since caries disease progression is slow [31], it does not seem to trigger an acute inflammatory response such as bleaching probably does [16, 21, 30]. Thus, the presence of COX-2 in the pulp of carious teeth does not necessarily mean that the inflamed pulps of bleached teeth will express this enzyme immediately after bleaching.

Another explanation for the lack of efficacy of etoricoxib in preventing TS is that several other inflammatory mediators [32] are likely to be involved in the inflammatory reaction in the pulp tissue, which leads to pain and symptoms of neurogenic inflammation. For instance, bradykinin [33] and substance-P have long been known to be involved in the process of pulp pain and inflammation [17, 34]. Unfortunately, etoricoxib cannot prevent the production of these mediators. If many mediators are synergistically acting to produce both pain and inflammatory reaction after bleaching, an anti-inflammatory agent that inhibits several initial inflammatory events, such as the glucocorticoids [35], may be more effective to reduce the TS arising from bleaching. Glucocorticoids are known to inhibit the expression of multiple inflammatory genes (cytokines, enzymes, receptors, and adhesion molecules) and inhibit the transcription of several cytokines that are relevant in inflammatory diseases [36]. This should be the focus of future clinical investigations that attempt to reduce bleaching-related TS.

It is known that dental pulp is densely innervated with sensory afferents with conduction velocities in the Aβ, Aδ, and C-fiber range [37]. One may hypothesize that hydrogen peroxide may cause direct cellular damage to nerve cells via free radicals and other reactive oxygen species [38] triggering nerve fiber depolarization. In fact, hydrogen peroxide can, under certain conditions, react with a variety of cellular components, which include lipid peroxidation of membrane protein and nucleic acid oxidation [39, 40]. If this is the cause of TS, the use of an anti-inflammatory drug, such the one investigated in the present study, would not reduce the pain experience. Other alternative approaches such as the use of anti-oxidant drugs, not yet investigated, and the use of desensitizers [3] would be more effective. The latter cannot reduce the cell damage, but it can reduce the excitability of the intradental nerves [41, 42]. A potassium nitrate agent used before bleaching was shown to reduce the experience of TS [3] since it penetrates through the enamel to travel to the dentin-pulp complex where it creates a calming effect on the nerve by reducing the transmission of nerve impulses [41, 42].

The efficacy of any drug is dependent on the selected dose. Thus, one cannot rule out the fact that a low dose could be the reason for the lack of efficacy of the drug in the present investigation. An earlier study evaluating the effect of different doses of etoricoxib on the acute pain resulting from dental surgery reported lower pain with the use of higher doses [43].

In regard to the bleaching outcome, the results of this study indicated that both groups demonstrated equivalent and significant tooth color enhancement when compared with baseline (Table 1). It is difficult to compare color change after in-office bleaching with existing literature due to the different methods of measurement (shade guides and spectrophotometers) and different units of measurement (CIELab system, SGU, etc.) used. However studies that used 35 % hydrogen peroxide and reported their results in SGU usually observed an overall color change of 5 to 8 SGU after two bleaching sessions [3–9], which is in agreement with the results of the present investigation.

Finally, one could not omit mentioning that the small sample size is a clear limitation of the present study. The study was designed to find a high effect size, i.e., reduction of approximately 50 % in the absolute risk of TS between participants from the placebo and the experimental group. Thus, we can conclude that an effect size as large as this was not observed with a power of 80 %, but we cannot rule out the fact that smaller effect sizes do exist. Use of the same experimental design to conduct studies with larger sample sizes should be encouraged to rule out this hypothesis. Moreover, the selected sample was mainly composed of young participants, which also limits the ability to generalize our findings to the general population of older adults.

Conclusions

Within the limitations of our study, we conclude that the use of etoricoxib 60 mg does not reduce the experience and intensity of TS.

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Conflict of interest The authors declare that they have no conflict of interest.

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