Evaluation of the effects of photobiomodulation (808 nm) on pain and quality of life of diabetic neuropathy patients

Avaliação dos efeitos da fotobiomodulação (808 nm) na dor e na qualidade de vida de pacientes com neuropatia diabética

Evaluación de los efectos de la fotobiomodulación (808 nm) sobre el dolor y la calidad de vida de los pacientes con neuropatía diabética

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Milena Valdinéia da Silva Leal
ORCID: https://orcid.org/0000-0003-4064-5316
Universidade do Vale do Paraíba, Brazil
E-mail: milenaleal@bol.com.br

Mário Oliveira Lima
ORCID: https://orcid.org/0000-0002-0678-6011
Universidade do Vale do Paraíba, Brazil
E-mail: mol@univap.br

Davidson Ribeiro Costa
ORCID: https://orcid.org/0000-0002-9750-5675
Centro de pesquisa Avançada em Fototerapia, Brazil
E-mail: drnrbcosta@hotmail.com

Renata Amadei Nicolau
ORCID: https://orcid.org/0000-0002-7687-7963
Universidade do Vale do Paraíba, Brazil
E-mail: renatanicolau@hotmail.com

Luana Aparecida Pilato Ribeiro
ORCID: https://orcid.org/0000-0002-2317-8835
Centro de pesquisa Avançada em Fototerapia, Brazil
E-mail: Luanapilato@yahoo.com.br

David Ribeiro Costa
ORCID: https://orcid.org/0000-0002-4188-1321
Centro de pesquisa Avançada em Fototerapia, Brazil
E-mail: profdavid8@gmail.com

Teresa Marly Teles de Carvalho
ORCID: https://orcid.org/0000-0002-6102-9662
Universidade do Vale do Paraíba, Brazil
E-mail: tmarly@bol.com.br

Kelson Nonato Gomes da Silva
ORCID: https://orcid.org/0000-0002-3162-038X
State University of Piauí, Brazil
E-mail: tkelson@bol.com.br

Diego Rodrigues Pessoa
ORCID: https://orcid.org/0000-0002-8981-673X
Piauí Higher Education Association, Brazil
E-mail: fisio.diegorodrigues@gmail.com

Emilia Angela Lo Schiavo Arisawa
ORCID: https://orcid.org/0000-0003-3526-3890
Universidade do Vale do Paraíba, Brazil
E-mail: mirela@univap.br

Abstract
Diabetic neuropathy (DN) is one of the main complications of diabetes mellitus (DM), responsible for a high morbimortality rate and burdening public health resources. Photobiomodulation has proven to be effective in relieving pain, reducing the inflammation, and improving vascularization. We report an evaluation of the effectiveness of photobiomodulation for the relief of pain and to improve the quality of life in patients with diabetic neuropathy. A total of 30 diabetic volunteers with DN were randomly divided into three groups: control, photobiomodulation (PBM), and placebo (P-PBM). Those in Group control were instructed to take diabetic neuropathy medication for 30 days. The PBM group received laser photobiomodulation treatment with the following protocol: three sessions per week for 30 days, totaling 12 applications (wavelength, 808 nm; energy density, 12 J/cm²), in the of following nerves: tibial medial plantar, own plantar digital, common plantar digital, superficial fibular, deep fibular, sciatic, saphenous, and...
common fibular. Patients in the P-PBM Group were submitted to the PBM protocol, but with the device switched off. Before and after applying the therapeutic protocols, all volunteers were subjected to pain evaluations. The results showed a statistically significant difference between the groups (p < 0.05). The PBM group confirmed an analgesic effect directly related to the use of the photobiomodulation, whilst the patients in group control and P-PBM, did not present significant results. The study demonstrated that laser photobiomodulation is effective in significantly reducing pain and improving the quality of life of patients with diabetic neuropathy.

Keywords: Diabetes mellitus; Diabetic neuropathies; Pain; Photobiomodulation.

1. Introduction

Diabetes mellitus (DM) is a metabolic syndrome characterized by the prevalence of hyperglycemia, caused by a deficiency in insulin secretion and/or its inability to adequately perform its functions (De Abreu & Oliveira, 2015). It was estimated that 120 million people had DM worldwide and it is expected that by 2025 this number will reach 300 million (Telo et al., 2016). DM is a chronic disease of multiple etiology, with long-term consequences that can lead to dysfunction, damage, or failure of several organs. It is associated with increased mortality due to the high risk of developing acute and chronic incapacitating complications (Duncan et al., 2017).

DM complications are degenerative in nature and usually occur between 5 and 10 years after the onset of the disease (De Abreu & Oliveira, 2015; Telo et al., 2016). Among the complications, diabetic neuropathy (DN) is highlighted (Duncan et al., 2017).
al., 2017; Aslam & Rajbhandari, 2014). DN is considered to be a set of syndromes with several clinical and subclinical manifestations, leading to the occurrence of an extensive neurological lesion involving the sensorimotor and autonomous components of nervous system (Aslam & Rajbhandari, 2014; Yoo et al., 2013). This is associated with atherosclerosis of small vessels, making the individual susceptible to the development of ischemic and infectious problems in extremities, leading to ulceration, gangrene, and even limb amputation (Aslam & Rajbhandari, 2014; Yoo et al., 2013).

DN is considered one of the most frequent chronic complications of DM, affecting approximately 50% of type II diabetes patients, who represent the major source of morbidity and mortality among diabetic patients (Davies et al., 2006; Tesfaye & Selvarajah, 2012). The consequences of peripheral nerve injury arise from microangiopathies, axonal loss and axonal atrophy (Head, 2006). All nerve fibers can be injured, but the most affected are the small myelinated and non-myelinated fibers, that conduct pain and temperature (Head, 2006; Sehlo et al., 2016).

The main factor for the prevention of DN is the metabolic control of DM by inhibiting the appearance of lesions as well as their intensity and extent (Telo et al., 2016). In addition, pharmacological and non-pharmacological measures have been indicated for the treatment and improvement of established neuropathy (Dworkin et al., 2007). The current treatment of DN is symptomatic, to relieve pain by administering various systemic analgesics (Dworkin et al., 2007). Several non-pharmacological treatments have also been proposed, including acupuncture, static and pulsed magnetic field therapies, photobiomodulation (PBM) and various electrotherapies (Çakici et al., 2016; Volchegorskii, 2017). Among the different options, PBM has been used as an alternative to conventional therapeutic resources (Wróbel et al., 2008; Cg et al., 2015).

Large-scale testing with PBM demonstrated improvement in the inflammatory process, reduction of edema, minimization of pain symptomatology, and biostimulation of cellular activity (Cg et al., 2015, De Freitas & Hamblin, 2016). The results of the studies by Freitas and Hamblim (2016), Wang et al. (2016), Costa et al (2017) and Costa et al. (2021) showed that the action of PBM occurs from the absorption of light by mitochondrial chromophores (cytochrome c oxidase), which act as photoreceptors in mitochondrial tissue. Use of anti-inflammatory medications can cause liver and kidney damage, as well as drug interactions, among other consequences, with high costs for the health system in Brazil.

The aim of the present study was to evaluate the effects of photobiomodulation (PBM) for pain relief and quality-of-life improvement in patients with diabetic neuropathy.

2. Methodology

This clinical trial is of an interventional nature, in which the methodology of our previous study was followed (da Silva Leal et al., 2020). The present study was submitted and approved by the Ethics Committee of the State University of Piauí (CAAE No. 70966117.5.0000.5209). The study consisted of a controlled, randomized, prospective, interventional, and quantitative clinical study. This study was developed in the Physiotherapy Service in the Hospital Getúlio Vargas (HGV), Dirceu Mendes Arcoverde Outpatient Care, in Teresina-PI, from February 2018 to February 2019.

The number of patients was calculated using the online platform of the Epidemiology and Statistics Laboratory of the University of São Paulo (LEE-USP), including the mean and standard deviation values of the primary outcome variable (pain) according to the article by Cg et al. (2015) The calculation was performed using ANOVA, with significance of 5% and test power of 95%. According to the sample calculation, 30 patients with NP should be divided into 3 groups with 10 individuals each.

A total of 50 patients were evaluated and selected by anhe enzyme citrate synthase acts on the Krebs cycle, promoting the production of adenosine triphosphate (ATP). In addition, Pessoa et al. (2018) emphasized that photobiomodulation promotes inhibition of arachidonic acid, with the consequent reduction of cyclooxygenase-2 (COX-2) enzyme expression and prostaglandin E2 production, which modulate the inflammatory response. Absorption of light emitted
by PBM favors the temporary release of nitric oxide, reducing local ischemia. These actions result in anti-inflammatory action from the absorption of LILT.

PBM presents advantages over other conventional treatment methods, among which we can mention anti-inflammatory, analgesic and scar actions. In addition, the con angiologist doctor based on eligibility criteria (inclusion and exclusion). Inclusion criteria were: diagnosis of type II diabetes uncontrolled, DN in the lower limbs (leg and feet), glycemic values between 150 and 350 mg/dL and aged between 45 and 60 years. The exclusion criteria were: unstable glycemic control and/or medical conditions such as cancer, active/untreated thyroid disease, peripheral vascular diseases (PVD), vascular insufficiency (claudication, skin discoloration, ulceration), significant renal or hepatic disease, pregnancy, alcohol or illicit drug abuse, and other neurologic diseases.

Thirty volunteers who met the inclusion and exclusion criteria were selected. The volunteers were instructed about the procedures and objectives of the study and signed the Informed Consent Form (ICF). Os 20 unselected patients had alterations in glycemic indexes (n = 8), vascular insufficiency (n = 2), renal disease (n = 5) and peripheral vascular disease (n = 5). Thirty patients were randomly assigned to the groups: Control (n=10), Placebo Photobomodulation (P-PBM, n=10) and Photobiomodulation (PBM, n=10). Randomization was performed by the therapist, using a card system that maintains the complete randomization of subject's distribution to a given group. This form of randomization is simple and easy to implement in a clinical trial. Patient evaluation was performed by a blinded researcher. Only one researcher knew which group the patients were allocated to and performed all treatments. Another blind researcher performed all evaluations. The patients were informed about the treatment protocols.

Control group

The volunteers underwent the conventional treatment prescribed for DN including tricyclic antidepressants (amitriptyline hydrochloride 300 mg, produced by Neo Química (São Paulo, São Paulo-Brasil); ach tablet containing amitriptyline hydrochloride 25 mg, microcrystalline cellulose, sodium starch glycolate, silicon dioxide, dibasic calcium phosphate, FD&C No. 05 yellow lacquer dye, and magnesium stearate), anticonvulsants (Gabapentin 300 mg, manufactured by Ems.sigma Pharma LTDA (Hortolândia, São Paulo-Brasil); each capsule containing gabapentin 300 mg, povidone, and talc), and opioid drugs (tramadol hydrochloride 100 mg/ml, produced by Neo Química (São Paulo, São Paulo-Brasil); each mL of the oral solution containing tramadol hydrochloride 100 mg, glycerol, propylene glycol, sodium saccharin, sodium cyclamate, polysorbate 80, potassium sorbate, peppermint oil, and water, and 40 drops corresponded to 1 mL of the medicine).

Photobiomodulation (PBM) group

Volunteers in this group were submitted to PBM application as well as the conventional treatment described for group control. The parameters used are listed in Table 1. For the administration of PBM, the following biosafety standards were adopted: use of eye protection (patient and professional), light beam cover with transparent insufilm to avoid contamination and cleaning of the treatment table and the irradiated area with 70%.
Table 1 - Parameters of photobiomodulation.

| Parameters                          | P-PBM and PBM   |
|------------------------------------|-----------------|
| Wavelength (nm)                    | 808 nm          |
| Operation mode                     | Continuous wave |
| Average radiant power (mW)         | 100             |
| Aperture diameter (cm$^2$)         | 0.06            |
| Irradiated area (cm$^2$)           | 0.028           |
| Irradiance (W/cm$^2$)              | 1.666           |
| Radiant exposure (J/cm$^2$)        | 200             |
| Exposure time per point (s)        | 120             |
| Radiant energy per session (J)     | 12              |
| Number of applications             | 12              |

*Diodo laser: Easy Laser (DMC® equipaments Ltda, SP, São Carlos, Brazil), Continuous output.** Source: Authors.

For the PBM treatment, patients were instructed to remain in a comfortable position. Once local asepsis was performed, and laser photobiomodulation was applied using the RIWT/DMC. A total of 12 applications were done, three per week, in alternated days. Punctual contact was adopted with the pen held in a perpendicular position at equidistant points in the of following nerves: tibial (Figure 1A – blue), medial plantar (Figure 1A – black), own plantar digital (Figure 1A – orange), common plantar digital (Figure 1A – yellow), superficial fibular (Figure 1A – grey), deep fibular (Figure 1A – green), sciatic (Figure 1B – red), saphenous (Figure 1B – yellow) and common fibular (Figure 1B – green).

Figure 1. Schematic representation of the points of photobiomodulation application.
Placebo (P-PBM group)

The same protocol described for the PBM group was applied, with the laser device turned off to simulate photobiomodulation application.

Clinical evaluations

Volunteers were assessed both at baseline (pre-therapy) and after completion of therapeutic protocols (post-therapy). Personal data and medical history related to DM and DN were collected from all participants. To evaluate the efficacy of the clinical protocols proposed in this study, the following instruments were used: Visual Analog Pain Scale (VAS), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale e PainDETECT scale. To assess the quality of life, we used the Medical Outcomes Study 36 - Item Short - Form Health Survey (SF-36).

VAS scale: This is a useful and reliable instrument to evaluate pain intensity and quantify the perception of pain. A numerical scale from 0 to 10, in which zero (0) indicates an absence of pain and the worst possible pain is indicated as 10, is utilized. This instrument made it possible to evaluate the pain from the patient’s perspective (Costa et al., 2017).

LANSS scale: This instrument consists of seven questions and it was used to collect the patient’s history and physical examination information, as well as to obtain sensitivity and specificities of pain and diagnoses of neuropathic pain.

PainDETECT scale: This instrument reveals information on the diversity of pain manifestations and the complexity of the underlying biological mechanisms, such as the presence of allodynia or hyperalgesia. It questionnaire consists of seven questions that address the quality of pain symptoms. The adequate evaluation of pain and paresthesia is critical for verifying the efficacy of treatment protocols proposed in clinical practice as new therapeutic options for diabetic neuropathy.

Medical Outcomes Study 36 - Item Short - Form Health Survey (SF-36): This is method of general health assessment, originally created in the English language. It is easy to apply and understand, and consists of 36 questions covering the evaluation of eight components: functional capacity (10 questions), pain (2 questions), general health (5 questions), physical aspects (4 questions), vitality (4 questions), social aspects (2 questions), mental health (5 questions) and emotional aspects (3 questions). Eight domains were evaluated: functional capacity, limitations due to physical aspects, pain, general health, vitality, social aspects, limitations due to emotional aspects, and mental health. The SF-36 questionnaire was used to identify the meaning of quality of life for people with diabetic neuropathy, before and after treatment was carried out, to analyze the quality-of-life aspects most influenced by the disease and the participants’ degree of satisfaction with life (Costa et al., 2017).

Data were analyzed using Graphpad Prism v. 5. Kolmogorov-Smirnov normality test was applied to analyze the distribution of the sample data, followed by the non-parametric Wilcoxon test, applied for intra-group comparison (before and after treatment). Kruskal-Wallis test with Dunn's posttest was applied for intergroup evaluation. For all tests, a significance level of 5% (p < 0.05) was considered.

3. Results

Anthropometric and clinical characterization of patients

All patients in this study presented type II DM and DN. They also showed associated diseases such as systemic arterial hypertension, with blood pressure levels that fluctuated during the research, tending towards mild hypertension. None of them suffered from neoplasia or autoimmune diseases.

Table 2 demonstrate the homogeneity of the sample studied, indicating that the participants were hyperglycemic, with postprandial blood glucose levels of 223 to 247 mg/dL, two hours after a meal, according to criteria established by the World Health Organization (WHO). The mean body mass index (BMI) was 26.8, indicating that the individuals were slightly overweight, according to the BMI classification defined by the WHO, and the mean age of the patients was 66 years. Diagnosis of DN occurred in study participants between 12 and 17 years after onset of DM.
Table 2. Quantitative anthropometric data analysis results.

| Dataa,b | Control | P-PBM | PBM   | (P value) |
|---------|---------|-------|-------|-----------|
| Age (years) | 67 ± 2 | 69 ± 2 | 66 ± 2 | (0.680) |
| BMI     | 28 ± 2 | 29 ± 1 | 25 ± 1 | (0.416) |
| Glycemia (mg/dL) | 226 ± 16 | 247 ± 17 | 223 ± 14 | (0.521) |
| Disease duration (years) | 12 ± 1 | 13 ± 1 | 17 ± 2 | (0.397) |

aThe data is expressed as mean ± standard error. bIntergroup analysis: Kruskal-Wallis test with Dunn’s post-test (p > 0.05, not significant for all data). Source: Authors.

Evaluation of pain in patients with diabetic neuropathy

The results obtained with the VAS instrument, LANNS pain scale, and PainDETECT questionnaire, applied before and at the end of the protocols (30 days), are presented in Figure 2 A, B, and C, respectively. The degree of pain in the different patient groups was evaluated, and a statistically significant difference was observed in each instrument (VAS, LANNS, and PainDETECT), indicating reduction and relief of pain as a result of PBM application. By contrast, a comparison of the results obtained with the P PBM and Control groups, before and after application of the therapeutic protocols, revealed no statistically significant differences.

Figure 2. Result of pain analysis with VAS (A), Lanns (B) and Paindetect (C) instruments, between control, P-PBM and PBM groups. Intragroup analysis (Wilcoxon test): ** p <0.01. Intergroup analysis p <0.05 (Kruskall-Wallis test with Dunn's posttest): “a” vs Initial PBM, “b” vs final PBM, “c” vs Initial P-PBM, “d” vs Final P-PBM. Data expressed as mean ± standard error of the mean.

Figure 3 displays the results obtained from the SF-36 instrument applied before and after the clinical intervention (30 days). Control group did not reveal any statistically significant differences. Placebo group showed significantly lower values.
post-therapy regarding the vitality, social aspects, and mental health domains. On the other hand, all indicators evaluated by the SF-36 instrument showed improvement, with statistically significant values after PBM. The pre-therapy mental health domain was significantly higher in the PBM group compared to the control and placebo PBM groups, while the pain domain in the latter group was significantly higher compared to that of the control and the PBM groups, pre-therapy. Pain, general health, vitality, and social aspects domains of the PBM group post-therapy were significantly higher with respect to the corresponding domains of the other groups. The limitations due to emotional aspects domain of the PBM group, post-therapy, was higher than that of the control group, but there was no significant difference between the PBM and the placebo PBM group in this domain. In summary, PBM volunteers stood out in terms of improvements in their quality of life after the clinical intervention.

**Figure 3** - Radar graphs represent the assessment of quality of life with application of the SF-36 instrument. Wilcoxon statistical test comparing the initial versus final phase of each parameter in the different clinical protocols. *p < 0.05.*

Before treatment (blue) and after (red). The higher the number the better according to the SF-36. Source: Authors.

### 4. Discussion

The present study investigated the effects of photobiomodulation (PBM) for pain relief and quality-of-life
improvement in patients with diabetic neuropathy. Our results demonstrate that PBM was efficient in the control of neuropathic pain, contributing to improve the quality of life of diabetic patients. Several studies (Bashiri, 2013; Cidral-Filho, 2013; de Andrade et al., 2017) highlighted the importance of PBM in pain management in patients with diabetic neuropathy, as a complementary therapy to drug resources, due to its photobiomodulatory effects of low-level laser.

Gonçalves et al. (2010) proved that FBM is beneficial in reducing the inflammatory process, decreasing myelin sheath degeneration after sciatic nerve injury, minimizing painful stimuli from nerve tissue damage. Andrade et al. (2017) reported significant results in nerve tissue regeneration after PBM by eliminating the inflammatory picture and controlling neuropathic pain due to its photobiomodulatory effect.

The analgesic action induced by PBM can be explained by the modulation of inflammatory mediators. Release of beta-endorphin tends to limit the excitability of painful receptors and to eliminate pain sources. Pessoa et al. (2017) and Wang et al. (2018) emphasized that PBM irradiation does not promote significant changes in local cell temperature. This fact is confirmed when therapy is applied with appropriate dosimetric parameters comprising wavelength, power, energy and irradiation time. Considering the photophysical, photoelectric and photobiological effects, the results observed in our study in controlling neuropathic pain may have been induced by increased stimulation of mitochondrial photoreceptors, ATP production and microcirculation ativation, all these factors associated with an antiinflammatory response (Costa et al., 2021 B).

Feitosa et al. (2017) concluded that the analgesic effect on neuropathic pain control is directly related to the use of PBM, considering that at the end of treatment volunteers reported improvement in pain perception in relation to initial pain. These results were confirmed by the study by Carvalho et al. (2016), concluding that PBM was effective in relieving pain due to its anti-inflammatory action, increased neovascularization, and reduced morbidity due to DM.

PBM is effective in controlling neuropathic pain when employed in the near infrared electromagnetic spectrum (700 to 880 nm), with powers ranging from 70 to 100 mW and doses ranging from 7 to 12 J. This statement is reinforced by the results reported by Huang et al. (2009), who stated that near-infrared (808 nm) irradiation reduced neuropathic pain by releasing histamine, serotonin, bradykinin and prostaglandins, in addition to producing enzyme action modification, favoring tissue regeneration and pain reduction. Good control of neuropathic pain results obtained in this study were also observed by Andrade et al. (2016) The authors emphasized that radiations in the infrared electromagnetic spectrum (700 to 880 nm) are the most used to control this type of pain. Another key point is dose (energy) standardization, as higher dosages promote significant analgesia. However, further randomized controlled clinical trials are needed to establish the best clinical treatment protocol.

Pain conditions, especially chronic pain, are known to drastically reduce an individual's quality of life and lead to intense emotional changes, causing weakness and psychological distress (Andrade, 2016). Almeida et al. (2013) reinforced that ND causes profound changes in the lifestyle of its bearer, compromising self-esteem and self-image, negatively affecting their quality of life. In the present study, the beneficial results were confirmed by the SF-36 instrument that evaluates the quality of life in PBM group. All domains showed a statistically significant difference when comparing pre-therapy vs post-therapy evaluations in the pain, general health, vitality and social aspects domains.

Moreira et al. (2016) concluded in their study that after the use of FBM it was possible to verify that patients diagnosed with DM with presence of lower limb injuries showed improvement in quality of life levels, especially in the domains related to functional capacity and physical, social and emotional aspects. Feitosa et al. (2017) confirmed the physical, emotional and social suffering caused by DM complications, such as ulcerations and possible amputations. Thus, the study of quality of life acquires relevance in the scenario directed to health services and clinical practice, as an important factor for the decision-making process and determination of therapeutic benefit in public and private health services.

Yekta et al. (2011) used the SF-36 instrument to assess the quality of life of diabetics. They observed that the ability
to appreciate life, sleep quality and pain presented greater impairment in the group of patients with ulcers compared to the group without ulcers. This result is justified by the perpetuation of isolation and conditions related to the depressive state.

These findings are consistent with those presented by the authors (Cg et al., 2015; Feitosa et al., 2017) who confirmed the constant presence of depressive disorders and difficulties in interpersonal relationships associated with inability to walk. These factors generate physical dependence and, as a result, emotional disturbances.

Faria et al. (Faria et al., 2013) pointed out that investigations of the quality of life of diabetic patients, assessing the physical, emotional and social suffering caused by NP complications, may contribute to the better dimensioning with the care of this patient, aiming the integrality of health care and choice of better therapeutic practice.

In this sense, through the results of the present study and the specific literature, it is possible to infer that ILIBI promoted the analgesic and anti-inflammatory effects of PBM, in addition to other effects such as vasodilation, stabilization of hormone levels, spasmyotics and sedatives, among others, which may be beneficial for the treatment of NP.

The promising results obtained in the present study stimulate new clinical research, with the same methodological approach, to broaden the knowledge about the systemic effects after PBM in DN patients. Further randomized clinical trials in these patients are recommended, with assessment of muscle strength by surface electromyography (EMG), as well as sleep quality and psychological aspects (anxiety, stress and depression) to prove the effectiveness of PBM.

5. Conclusion

The results confirm the efficacy of PBM in treating patients with diabetic lower limb neuropathies. The benefits of this therapeutic modality were identified, such as the low potential for adverse reactions and the limited number of contraindications. It is noteworthy that the group submitted to PBM presented significant pain relief and improved quality of life. It is concluded that PBM is an effective non-pharmacological technique for the treatment of ND.

However, research with a larger number of volunteers would be necessary so that trends observed in the present study could be analyzed further.

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