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POST-THERAPEUTIC ANTIOXIDANTS-ASSOCIATED CHANGES IN THE CONCENTRATION OF INFLAMMATION AND CYTOPROTECTION MARKERS IN THE BLOOD OF PATIENTS WITH CHRONIC GENERALISED PERIODONTITIS

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Despite the successes achieved in the treatment of chronic periodontitis, the problem remains relevant and requires new approaches to drug therapy. In connection with the understanding of the role of oxidative stress in the pathogenesis of periodontitis, the additional inclusion of antioxidants in complex therapy is promising.

The aim of the work: laboratory and biochemical assessment of the effectiveness of complex therapy for chronic generalised periodontitis with the additional inclusion of the antioxidant drug with sodium selenite pentahydrate.

Materials and methods: 60 patients with chronic generalised moderate periodontitis (aged 40 to 65, including 35 women and 25 men) were divided into control and main groups. Patients in the main group were additionally included in complex therapy with the antioxidant sodium selenite pentahydrate.

Results: During the first 10 days (5 times), it was administered by intraoral bivalve transgingival electrophoresis (50 mcg/day), and then at the same dosage "per os" for 20 days. Before the start and after 30 days of treatment, markers of inflammation (IL-1β, TNF-α) and endogenous cytoprotection (HIF-1a and HSP70) were determined in the blood of patients by enzyme-linked immunosorbent assay. Statistical analysis was performed using the software package “STATISTICA® for Windows 6.0” (StatSoft Inc., No. AXXR712D833214FAN5), as well as “SPSS 16.0" and "Microsoft Excel 2003”. The results obtained demonstrate the promising potential of including sodium selenite pentahydrate in the complex therapy of chronic generalised periodontitis, as an important component of its antioxidant composition.

Keywords: chronic generalised periodontitis, complex therapy, antioxidants, endogenous cytoprotection, inflammation.

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ПОСТТЕРАПЕВТИЧНІ АНТИОКСИДАНТ-АСОЦІЙОВАНІ ЗМІНИ КОНЦЕНТРАЦІЇ МАРКЕРІВ ЗАПАЛЕННЯ ТА ЦИТОПРОТЕКЦІЇ У КРОВІ ПАЦІЄНТІВ ІЗ ХРОНІЧНИМ ГЕНЕРАЛІЗОВАНИМ ПАРОДОНТИТОМ

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Незважаючи на досягнуті успіхи в лікуванні хронічного пародонтиту, проблема залишається актуальною і потребує нових підходів до медикаментозної терапії. Розуміння ролі оксидативного стресу в патогенезі пародонтиту актуалізує додавання до комплексної терапії антиоксидантів. Метою дослідження було окреслено лабораторно-біохімічну оцінку ефективності комплексної терапії хронічного генералізованого пародонтиту за додавання антиоксиданту – препарату з діючою речовиною «натрію селеніту пентагідрат». У рамках дослідження обстежено 60 пацієнтів із цільовою патологією середнього ступеня тяжкості, які були розподілені на групи. Пацієнтам основної групи додатково здійснювалося додавання до комплексної терапії натрію селеніту пентагідрата у формі вищезазначеного препарату шляхом інтраорального трансгінгівального електрофорезу, потім у тому ж дозуванні per os. Діагностичними критеріями були рівні молекулярних маркерів IL-1β, TNF-α, HIF-1α і HSP70.

Ключові слова: хронічний генералізований пародонтит, комплексна терапія, антиоксиданти, ендогенна цитопротекція, запалення.

Introduction

Periodontal diseases are considered a health problem due to their high prevalence worldwide. Despite the success achieved in understanding the pathogenesis and treatment of inflammatory periodontal diseases in recent decades, the problem remains relevant. Currently, the treatment of periodontal diseases is not always successful due to a number of factors, including patients' failure to follow targeted medical instructions and recommendations, incomplete understanding of some subtle, highly specific links in the molecular mechanisms of inflammation, oxidative and nitrosative stress, and endogenous cytoprotection, which lead to the irrational selection of medications when planning and implementing treatment for periodontal patients [1].

Periodontal studies have identified specific microbial pathogens, including *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola,* which, in combination with moderately virulent organisms, form highly organised complex communities in the form of biofilms, initially present at

the supragingival level and, in later stages of the disease, at the subgingival level [2]. The presence of periodontal pathogenic biofilm stimulates the activation of signalling pathways associated with inflammation in gingival fibroblasts and the production of inflammatory cytokines (IL-1β, TNF-α, IL-6) and reactive oxygen species (ROS) [3]. Periodontal inflammation activates several pathways of ROS formation at once: activation of NADPH oxidase in neutrophils, activation of iNOS and increased NO production, mitochondrial dysfunction, synthesis of pro-inflammatory prostaglandins and thromboxanes due to increased expression of COX-2, the Fenton and Haber–Weiss reactions in the presence of excess divalent iron [4]. Excessive uncontrolled production of ROS against the background of antioxidant deficiency leads to the development of oxidative stress, which, according to current understanding, plays a significant role in the destruction of periodontal tissues and also reduces the effectiveness of anti-inflammatory, reparative and antimicrobial therapy [5]. The above material justifies the widespread use of antioxidants for the treatment of chronic periodontitis in combination with antiseptics, antibiotics, anti-inflammatory and reparative drugs. In modern periodontology, antioxidants of plant origin (resveratrol, quercetin, green tea polyphenols), alpha-tocopherol, and thiotriazoline are widely applied [6]. However, the lack of clear guidelines for the use of antioxidants at different stages of treatment depending on their mechanism of action, their insufficient effectiveness and side effects necessitate both the development of new antioxidant agents and the use of various drugs with antioxidant activity that have not previously been used in periodontology. In particular, because periodontology has been separated into an independent dental specialisation (Ministry of Education and Science of Ukraine ORDER 15.02.2022 No. 293 "On Approval of Amendments to the Reference Book of Qualification Characteristics of Professions of Employees. Issue 78 Health Care"), there are grounds for developing new clinical protocols to ensure effective activity in the professional legal field. Selenium compounds, which have significant antioxidant, anti-inflammatory and cytoprotective activity, are of interest. In experimental studies, we have demonstrated the effectiveness of sodium selenite pentahydrate in experimental chronic periodontitis [7; 8]. The target selenium-containing drug is approved for clinical use and registered in Ukraine (UA/8796/02/01 dated 05.07.2019).

The objective of the study was to conduct laboratory and biochemical assessment of the effectiveness of complex therapy for chronic generalised periodontitis with the additional inclusion of a drug antioxidant with the active ingredient "sodium selenite pentahydrate".

Materials and Methods

In this study, we examined a group of 60 patients (35 women and 25 men) with chronic generalised periodontitis (CGP) of moderate severity.

The patients ranged from 40 to 65 years of age. We also examined 30 relatively healthy patients (with intact periodontium) during a preventive examination by a dentist. The selection, dynamic examination and multimodal treatment of patients diagnosed with CGP and intact periodontium were carried out at the Specialised Dental Centre of the University Clinic of Zaporizhzhia State Medical and Pharmaceutical University, as well as at the clinical base of the Department of Propaedeutic and Surgical Dentistry of ZSMU, the "Chertov Clinic" Dental Implantation Centre (Zaporizhzhia). All patients with CGP were divided into two groups: the main group and the control group, with 30 people in each, depending on the complex drug therapy that was carried out. When including patients in the study, the selection criteria were the presence of chronic generalised periodontitis and voluntary informed consent to examination and complex treatment in the form of a unified document, which was drawn up in advance by the researcher and scientific supervisors. Written informed consent with a personal signature was obtained from all patients who participated in the study. In turn, the exclusion criteria were the presence of acute or exacerbated chronic infectious diseases, autoimmune diseases, acute allergic reactions to therapy components, oncological diseases and ongoing chemotherapy, mental illness, pregnancy, long-term treatment with hormonal drugs, pituitary and thyroid diseases, and individual intolerance to one or more drugs. Participants were informed of their randomisation group assignment during the initial consultation visit.

Patients with CGP in both groups received standardised comprehensive non-drug and drug therapy for 3 months. Non-drug therapy consisted of professional oral hygiene (mechanical treatment of tooth surfaces, polishing, piezoelectric ultrasonic scaling with supragingival and subgingival working tips), Vector system periodontal therapy, closed (for periodontal pockets less than 5 mm deep) and open curettage (for periodontal pockets more than 5 mm deep) with GRACEY curettes manufactured by Hu-Friedy, as well as periodontal splinting of teeth in a physiological orthotopic position to level their pathological mobility (II-III degree) using special elements – glass fibre ligatures on photopolymer fixation. Drug therapy included anti-inflammatory agents applied topically and per os, antiseptic agents applied topically in the form of dental gels or rinses, as well as medicinal preparations in the form of gels or pastes based on propolis and solcoseryl. In addition to the main treatment, patients in the main group received sodium selenite pentahydrate (manufactured by Biosyn Arzneimittel GmbH, Germany) during the first 10 days (5 times) using intraoral transgingival electrophoresis applied to both jaws (50 μg/day), and then in the same dose internally for 20 days. The ZAPOVIT POTIK-01M device manufactured by BIOMED LLC (Ukraine) was used for electrophoresis. Sodium selenite pentahydrate was diluted in physiological solution with the addition of 0.5M phosphate buffer pH 6.8. Jumper cables and electrodes with disposable carbon conductive pads were used. The current strength was 5 mA for 15 minutes. The drug was administered from the negative pole.

Bioethical aspects of the study

The study was conducted with the consent of patients in accordance with the basic standards of GCP (1996), the European Convention on Human Rights and Biomedicine of 04.04.1997, and in accordance with the principles of the Helsinki Declaration in its latest edition, adopted at the 64th General Assembly of the World Medical Asso-

ciation (WMA) in Fortaleza, Brazil, in October 2013 [9]. This study was approved by the Bioethics Committee of Zaporizhzhia State Medical and Pharmaceutical University (protocol No. 3 of 12.06.2023). Before the start of the study, all patients were explained what the examination and complex therapy entailed. All participants in this study gave their consent to the processing of their personal data.

Blood sampling and preparation of biological material

Before and after 30 days of drug treatment, blood was taken from the elbow vein of patients in all groups and placed in a tube with EDTA anticoagulant. Plasma was separated from the blood by centrifugation in an Eppendorf-5804R centrifuge (Eppendorf, USA) at 1500 rpm for 20 minutes (T = 22 °C) [10].

Immunoenzymatic analysis

The concentration of HIF-1α was determined in plasma using the solid-phase enzyme-linked immunosorbent assay (ELISA) method. Human HIF-1α (Hypoxia Inducible Factor 1 Alpha) ELISA Kit # E – EL – H 6066 (Elabscience, USA) was used in accordance with the instructions provided with the kit. The concentration of heat shock protein HSP-70 was determined by immunoassay in blood plasma using the HSP-70 ELISA kit: Human Heat Shock Protein 70 ELISA Kit # MBS 760396 (MyBioSource, Canada) in accordance with the instructions provided with the kits. The content of IL-1β was determined in blood plasma using a solid-phase enzyme-linked immunosorbent assay (ELISA) with the Human IL-1β ELISA Kit # RAB 0273 (Merck KGaA, Darmstadt, Germany) in accordance with the instructions provided with the kits. The TNF-α content was determined in blood plasma using a solid-phase enzyme-linked immunosorbent assay (ELISA) with the Human TNF-α (Tumor Necrosis Factor Alpha) ELISA # E-EL-H0109 test kit (Elabscience, USA) in accordance with the instructions provided with the kits. These analyses were performed on a fully functional tablet immunoassay analyser (SIRIO-S, Seac, Italy).

Statistical analysis

All research data obtained were statistically processed using the STATISTICA® for Windows 6.0 software package (StatSoft Inc., No. AXXR712D833214FAN5), as well as SPSS 16.0 and Microsoft Excel 2003. The arithmetic mean (M) and the error of the arithmetic mean (m) were calculated. To identify intergroup and intragroup differences, Student's t-test and Fisher's angular transformation were used. Individual statistical procedures and algorithms were implemented in the form of specially written macros in the corresponding programs. For all types of analysis, differences were considered statistically significant at $p<0.05$.

Research results and their discussion

A dental examination of relatively healthy patients (intact periodontium) did not reveal any signs of bleeding, tooth mobility, or gum inflammation in this group. An examination of patients in the main and control groups before treatment revealed visual changes in the gums (swollen, cyanotic, pasty: edged, loosely attached to the teeth, disruption of the gum relief), the presence of pathological pockets (up to 5 mm) with serous and serous-purulent exudate, hard and soft dental deposits, pathological tooth mobility, as well as other signs of inflammation. That is, patients in the main and control groups had clinically confirmed chronic generalised periodontitis of moderate severity. Immunoenzymatic analysis of the blood plasma of patients with CGP in the main and control groups before the start of the study revealed a significant increase in inflammation markers and an increase in endogenous cytoprotection markers. Thus, in the blood of patients with CGP in both groups before the start of treatment, an increase in TNF-α was found by 4.48–4.16 times compared to the group of relatively healthy patients ($p < 0.05$), an increase in IL-1β 5.1–4.9 times compared to the group of relatively healthy patients ($p < 0.05$) (Table 1).

An increase in the blood of patients with CGP in both groups of markers of endogenous cytoprotection HIF-1α 1.82–1.78 times and HSP70 39.1% and 35.4% compared to the group of relatively healthy patients ($p<0.05$) was *also* established (Table 2).

After 30 days of comprehensive non-drug therapy for periodontal disease (removal of dental deposits and plaque, rational hygiene, curettage of periodontal pockets, vector therapy) and drug therapy (use of antiseptic, anti-inflammatory and reparative drugs), a decrease in the symptomatic manifestation of chronic periodontitis was recorded. Thus, in patients of both groups, there was a reduction in hyperemia, bleeding gums, and bad breath disappeared. At the same time, we determined that in the main group, whose patients additionally received an antioxidant in the form of sodium selenite pentahydrate (50 mcg/day, by electrophoresis and internally), the reduction in symptoms of chronic periodontitis was more pronounced. Thus, in patients in the main group, the additional administration of sodium selenite pentahydrate as part of complex therapy led to a significant reduction in the depth of periodontal pockets (to 2 mm, and in the control group to 3–4 mm), cessation of active exudation from them and epithelialisation of their bottom, minimisation of gum bleeding. A more pronounced reduction in tooth mobility was also noted in the main group 30 days after complex therapy against the background of a more pronounced improvement in the clinical picture of the gums than in the control group

Table 1

Inflammation markers in the blood of patients with CGP before and after 30 days of drug treatment

Patient groups	TNF-α, pg/ml	IL-1β, pg/ml
Relatively healthy (intact group) (n = 30)	56.2 ± 3.3	0.92 ± 0.05
Control group upon admission (n = 30)	234.3 ± 9.5[1]	4.7 ± 0.14[1]
Main group upon admission (n = 30)	252.0 ± 14.2[1]	4.5 ± 0.22[1]
Control group after treatment, 30 days (n = 30)	112.5 ± 7.5[1*]	2.2 ± 0.03[1] *
Main group after treatment (Sodium selenite pentahydrate) (n = 30)	87.0 ± 7.6[#] *	1.7 ± 0.05[#] *

Table 2

Cytoprotection markers in the blood of patients with CGP before and after 30 days of drug treatment

Patient groups	HIF-1α , pg/ml	HSP70, pg/ml
Relatively healthy (intact) group (n = 30)	100.2 ± 8.7	80.5 ± 6.3
Control group upon admission (n = 30)	182.3 ± 11.5[1]	112.3 ± 8.7[1]
Main group upon admission (n = 30)	178.0 ± 10.2[1]	109.1 ± 7.4[1]
Control group after optimised treatment for 30 days (n = 30)	188.5 ± 12.2[1]	123.7 ± 11.5[1]
Main group after improved treatment ("Sodium selenite pentahydrate") (n = 30)	224.0 ± 11.6[#] *	287.7 ± 12.4[#] *

Note:

[1] — The indicators are statistically significant in relation to the data of the intact group ($p < 0.05$).

[*] — Indicators are statistically significant in relation to pre-treatment data ($p < 0.05$).

— indicators are statistically significant in relation to the control group data ($p < 0.05$).

(a denser mucous membrane that closely adhered to the neck of the tooth, was less swollen, and no difference in colour from intact gums). Immunoenzymatic blood tests of patients in the control and main groups 1 month after complex treatment of GHP also showed improvement – a reduction in inflammation and an increase in endogenous cytoprotection mechanisms. The most pronounced positive changes were observed in patients in the main group, who additionally received sodium selenite pentahydrate. Thus, in patients in the main group, with the additional appointment of a targeted antioxidant drug in the complex therapy of CGP, a significant decrease in the concentration of TNF-α in the blood (by 65.4%) was observed compared to the indicators before treatment. In the control group, the level of TNF-α decreased by 52.1% compared to the data at the beginning of treatment ($p < 0.05$). Patients in the main group also showed a decrease in blood IL-1β concentration (62.2%) compared to pre-treatment levels ($p < 0.05$), while in the control group this indicator decreased by 51.1% ($p < 0.05$). The concentration of TNF-α and IL-1β in the blood of patients with CGD in the main group after 30 days of treatment was lower than the concentration of TNF-α and IL-1β in the control group for the same observation period ($p < 0.05$), indicating a significant increase in the anti-inflammatory effect of complex therapy due to the inclusion of a drug with the active ingredient sodium selenite pentahydrate. Immunoenzymatic analysis revealed a 25.8% increase in the concentration of HIF-1α in the blood of patients in the main group, which was observed 30 days after treatment ($p < 0.05$) and was 2.24 times higher than the values in the intact group ($p < 0.05$). In the blood of patients in the main group, the additional introduction of an antioxidant drug into complex therapy also led to an increase in HSP70 cytoprotection after 30 days of treatment by 163.9% ($p < 0.05$) and by 257.4% compared to intact values ($p < 0.05$). In the control group of patients with CGP who received standard therapy without prior antioxidant modification, no significant changes in the concentration of HSP70 and HIF-1α in the corresponding blood were found before and after treatment. The results obtained indicate intensive activation of endogenous cytoprotection mechanisms after complex therapy of CGP due to the inclusion of a targeted selenium-containing drug (active ingredient sodium selenite pentahydrate).

Chronic generalised periodontitis is an inflammatory disease that affects the tissues supporting the teeth and ultimately causes their loss. Currently, the aetiology of periodontitis is characterised by both general dysbiosis of the host and focal dysbiosis of the oral microbiota. Periodontal pathogenic bacteria and their waste products trigger a complex molecular-genetic cascade mechanism of activation of immune and inflammatory responses, initiation of oxidative stress, mitochondrial dysfunction, and apoptosis. Lipopolysaccharides of periodontal pathogenic bacteria cause the production of pro-inflammatory cytokines [11].

In addition, actinobacillus actinomycetemcomitans, the causative agent of aggressive periodontitis, increases IL-1β expression in human mononuclear leukocytes and macrophages. Leukotoxin, an important virulence factor that affects leukocytes, rapidly activates Caspase-1 and thus causes massive secretion of IL-1β in human monocytes and macrophages. The NLRP3 inflammasome, reactive oxygen species, and cathepsin B may be involved in this process. Proinflammatory cytokines – TNF-α, IL-6, IL-17, and especially IL-1β lead to inflammation and damage to periodontal tissues. IL-1β promotes bone resorption and induces the production of proteases and caspases, as well as matrix metalloproteinases (MMP-9, MMP-2, MMP-3). Matrix metalloproteinases promote the degradation of the extracellular matrix and lead to bone resorption and tissue destruction. IL-1β increases the expression of matrix metalloproteinases in various cell types involved in periodontal inflammation, including osteoblasts, osteoclasts, neutrophils, and cementoblasts in human periodontal ligament cells and gingival fibroblasts [12; 13]. Elevated levels of IL-1β and TNF-α are often found in the saliva, gingival crevicular fluid, and blood of patients with periodontitis compared to healthy control subjects. There is a positive correlation between IL-1β and TNF-α concentrations and periodontal pocket depth, bleeding, and tooth mobility in CGP. Moreover, high concentrations of IL-1β in patients with chronic periodontitis can have a negative systemic effect on the cardiovascular and endocrine systems: increasing the risk of diabetes mellitus, ischaemic heart disease, chronic heart failure, and arterial hypertension. Experimental studies have shown that chronic periodontitis in laboratory animals is accompanied by persistent changes in the expression of molecular markers of endogenous cytoprotection – HSP70 and HIF-1 [14; 15]. The role of HSP70 chaperone proteins has been well studied and consists in protecting cells from oxidative and nitrosative stress, apoptosis, infection, pyroptosis, and inflammation. HSP70 has

a positive effect on mineral metabolism, activates and regulates compensatory energy shunts during tissue hypoxia and ischaemia, prolonging the physiological effect of anti-hypoxic factors (HIF) [16]. In periodontal inflammation, HSP70 is expressed in response to increased IL-1β concentrations and acts as an endogenous cytoprotector. However, extremely high concentrations of IL-1β and TNF-α limit HSP70 expression or even cause its deprivation. Depending on the severity of chronic periodontitis, HSP70 levels may be either moderately elevated (mild to moderate) or decreased (severe) [17]. Comprehensive clinical and experimental data on the role of HIF-1α in inflammatory periodontal diseases have also been obtained. HIF-1α expression in periodontitis is triggered in response to increased levels of pro-inflammatory cytokines (IL-1β, TNF-α, IL-17) and NO. In turn, HIF-1α plays a protective role in periodontitis by enhancing immune defence, increasing the expression of VEGF and eNOS, and stimulating erythropoiesis. It is also known that HIF-1α in extreme cellular conditions, as well as in inflammation and infection, can positively influence energy metabolism by activating the compensatory malate-aspartate shuttle mechanism [18]. HIF-1α expression is closely related to the severity of inflammation, the concentration of pro-inflammatory cytokines and ROS. Elevated concentrations of IL-1β begin to inhibit HIF-1α mRNA expression and then reduce the level of HIF-1α protein itself in periodontitis, leading to a disruption of endogenous cytoprotection. Mild to moderate periodontitis leads to an increase in fibroblast-like and leukocyte-like cells expressing HIF-1α. In patients with periodontitis of this severity, increased concentrations of HIF-1α, VEGF, and TNF-α have been reported in periodontal pockets. More severe forms of CPG lead to a decrease in HIF-1α expression [19].

In this regard, pharmacological modulation of HIF-1 expression and prolongation of its "lifetime" in periodontitis is considered a promising direction in the treatment of inflammatory periodontal diseases. This approach not only reduces inflammation but also reduces local ischaemia by improving the energy metabolism of periodontal tissues – more rational use of pO_2 by switching to more economical ways of ATP synthesis. Pharmacological modulation of HIF-1 also enhances glycolytic metabolism, which is necessary for B-cell development and T-cell metabolism. This is due to the influence of HIF-1 on the mechanisms of pyruvate dehydrogenase expression in periodontal tissues. Pharmacological modulation of HIF-1α increases bone tissue regeneration, improves mineralisation and the osteogenic potential of periodontal ligament stem cells. It is known that an increase in HSP70 levels and prolongation of the "lifetime" of HIF-1α can be achieved through glutathione-dependent mechanisms under the action of selenium derivatives. Selenium derivatives also have a positive effect on the expression of glutathione peroxidase, inhibit the peroxidation of cell membrane phospholipids, and reduce the concentration of pro-inflammatory metabolites of arachidonic acid [20].

Conclusions

Based on molecular-biochemical and clinical studies, it has been established that the additional inclusion of an antioxidant based on sodium selenite pentahydrate (50 μg/day, 5 sessions of electrophoresis, then internally) is effective in the complex treatment of chronic generalised periodontitis.

The additional inclusion of a targeted selenium-containing drug in the complex treatment of CGP potentiates and accumulates the anti-inflammatory effect of therapy, as evidenced by a more pronounced decrease in IL-1β and TNF-α in the blood of patients after 30 days of treatment ($p < 0.05$) compared to the control group.

The inclusion of sodium selenite pentahydrate leads to the activation of endogenous cytoprotection mechanisms after 30 days of complex treatment of CGP – an increase in the concentration of HSP70 and HIF-1 ($p < 0.05$) compared to the data of patients in the control group.

The results obtained demonstrate the promise of using preparations based on sodium selenite pentahydrate and derivative pharmacological configurations as an important component of the antioxidant component of complex therapy for chronic generalised periodontitis.

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