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Evaluation of Effects of Melatonin on Myofascial Pain: A Preliminary Study

Melatoninin Miyofasiyal Ağrı Üzerine Etkilerinin Araştırılması: Ön Çalışma

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This study was presented as an oral presentation at International Hippocrates Congress, October 9-10, 2022, Online.

ABSTRACT Objective: To compare effects of melatonin with that of nonsteroidal anti-inflammatory drugs (NSAIDs) and behavioral therapy on patients sustaining myofascial pain. **Material and Methods:** A total of 45 patients were included and assigned into 3 groups; a melatonin (6 mg) group, a NSAID group and a behavioral treatment group. Preoperative, first- and third-month clinical parameters (masticatory muscle pain, temporomandibular joint region pain, facial pain, amount of mouth opening) were assessed using Research Diagnostic Criteria for Temporomandibular Disorders form retrospectively. Besides, sleep quality was assessed using Visual Analog Sleep Quality Scale at the same periods. **Results:** Following assessment of records of 300 (224 females and 76 males) patients 45 of them who met the inclusion criteria were included in the study. In the first month, facial pain decreased significantly in the melatonin group compared to other two groups (p1: 0.011; p2: 0.044). Mouth opening did not differ between the NSAID and the melatonin group (p>0.05), but was significantly lower in the behavioral treatment group (p1: 0.000; p2: 0.004; p<0.05). Considering muscle and temporomandibular joint pain, the melatonin group showed the least pain level. In the first and third months, sleep quality scores was did not show significant difference between the treatment groups (p>0.05), but increased significantly higher in the melatonin group compared to other two groups (p: 0.000; p<0.05). **Conclusion:** Complaints subsided in all the treatment groups. Melatonin can be considered as an agent that has analgesic and anti-inflammatory effects in myofascial pain. Further studies in this field are necessary those evaluate different regimens and routes of melatonin use.

Keywords: Temporomandibular joint; temporomandibular disorders; facial pain; melatonin

ÖZET Amaç: Miyofasiyal ağrılı hastalarda melatoninin etkilerinin nonsteroid antiinflamatuar (NSAİİ) ilaçlarla ve davranışsal terapiyle karşılaştırılmasıdır. **Gereç ve Yöntemler:** Bu çalışma için toplam 45 hasta; melatonin (6 mg) grubu, NSAİİ grubu ve davranışsal terapi grubu olmak üzere 3 gruba ayrıldı. Temporomandibular Rahatsızlıklar için Araştırma Teşhis Kriterleri formu kullanılarak preoperatif ve 1. ay, 3. ay klinik parametreleri (çiğneme kaslarında ağrı, temporomandibular eklem bölgesinde ağrı, yüz ağrısı, ağız açıklığı miktarı) retrospektif olarak değerlendirildi. Ayrıca, aynı periyotlarda uyku kalitesi Görsel Analog Uyku Kalite Skalası kullanılarak değerlendirildi. **Bulgular:** Bu çalışma için 300 (224 kadın, 76 erkek) hastanın değerlendirilmesi sonucu 45 hastanın dâhil edilmesine karar verildi. Birinci ayda melatonin grubunda fasiyal ağrı diğer 2 gruba göre anlamlı derecede azaldı (p1: 0,011; p2: 0,044). Ağız açıklığı miktarı, NSAİİ ve melatonin gruplarında farklı değilken (p>0,05), davranışsal terapi grubunda anlamlı derece azalmıştı (p1: 0,000; p2: 0,004; p<0,05). Çiğneme kasları ve temporomandibular eklem ağrısı açısından, en az ağrı seviyesi melatonin grubunda görüldü. Birinci ve 3. aylarda, uyku kalitesi gruplar arasında farklı bulunmadı (p>0,05), ancak; melatonin grubunda uyku kalitesindeki artış diğer 2 gruptan daha fazlaydı (p: 0,000; p<0,05). **Sonuç:** Bütün gruplarda hasta şikâyetlerinin azaldığı görüldü. Melatonin, analjezik ve antiinflamatuar etkileriyle miyofasiyal ağrıda kullanılabilecek bir ajan olarak düşünülebilir. Bu alanda melatonin farklı dozlarına ve uygulama şekillerine göre ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Temporomandibular eklem; temporomandibular düzensizlikler; fasiyal ağrı; melatonin

Myofascial pain (MP) is a chronic pain disorder where hypersensitive trigger points on masticatory muscles may cause pain. It is classified as a subgroup of temporomandibular disorders (TMDs) according to the American Academy of Orofacial Pain.[1,2] There are different modalities to treat MP including medications, oc-

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clusal appliances, muscle injections, physical therapy, and physiological support. Analgesic and anti-inflammatory drugs are commonly used as first-line therapies in the management of MP.[3-5]

Since TMDs are associated with inflammation, non-steroid anti-inflammatory drugs (NSAIDs) are usually effective pharmacotherapeutic options.[6] NSAIDs exert their anti-inflammatory effects by inhibiting cyclo-oxygenases, thereby preventing the formation of prostaglandins, one of the mediators of inflammation. However, long-term use of NSAIDs may have side effects on the stomach, duodenum, and other gastrointestinal systems organs.[6]

Myofascial TMD pain may be associated with sleep disorders such as insomnia and obstructive sleep apnea. Studies have demonstrated a high prevalence of sleep disorders in patients with TMDs and revealed a relationship between pain and sleep disturbance.[7,8] Loss of sleep has been shown to lower the pain threshold and lead to hyperalgesia.[9]

Melatonin is a neuroendocrine hormone released by the pineal gland and regulates circadian rhythm. As a potent antioxidant, melatonin is effective in sleep disorders, anxiety, regulating immunity, and anti-tumor action. It has also been shown to reduce pain and inflammation in numerous studies.[10,11]

The anti-nociceptive role of melatonin has been studied in animal models of acute inflammatory and neuropathic pain. Melatonin is believed to exert its analgesic effect by inhibiting endogenous opioids, ion channels, or peripheral prostaglandin synthesis.[12]

In clinical practice, melatonin is used to treat chronic diseases such as fibromyalgia, depression, anxiety, migraine, and irritable bowel syndrome and is also used to reduce anxiety in surgical operations and improve preoperative and postoperative analgesia.[13]

There is not enough information in the literature on the role of melatonin in antinociception or the use of melatonin as a potential analgesic/anti-inflammatory agent in MP. Considering the relationship between sleep disturbance and pain regulation of sleep may be beneficial for these patients. Therefore, the aim of this preliminary study was to investigate the effect of melatonin on patients sustaining MP.

MATERIAL AND METHODS

PATIENTS AND DATA

This study was approved by the Ethics Committee of İstanbul Medipol University (date: January 31, 2019, no: 10840098-604.01.01-E3633) in compliance with the Declaration of Helsinki. In this retrospective study, 300 patients referred to İstanbul Medipol University School of Dentistry from 2016 to 2019 with complaints of jaw muscle/joint pain and restricted/dysfunctional mouth opening were clinically examined. All the patients were evaluated by only one practitioner. MP was diagnosed according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMDs).[14] Patients diagnosed with MP underwent NSAID or melatonin therapy for one month and had 1- and 3-month follow-up data were included in the study.

The exclusion criteria were; a history of head/neck trauma; temporomandibular joint (TMJ) surgery; the presence of congenital deformity or degenerative joint disease; history of TMJ treatment or antidepressant use in the last 6 months; presence of any systemic disease that can prevent designated drug use or diagnosed psychiatric disorders and obstructive sleep apnea, corticosteroid or anticonvulsant drug use, and presence of active caries or pulpal lesions.

All patients were assessed using RDC/TMD Axis I Form.

Clinical data of the patients who met the inclusion criteria were collected. The three treatment groups were determined as follows: Group 1: Melatonin+behavioral therapy (BT); Group 2: NSAID (tenoxicam)+BT and Group 3: BT.

The following parameters were evaluated before treatment and at 1 and 3 months after initiation of the treatment.

Facial Pain: Based on the affected side and painful areas indicated by the patient on the RDC/TMD form. The presence of pain was recorded as none (0), right (1), left (2), or bilateral (3), and the area of pain was recorded as none (0), TMJ (1), muscles (2), or both (3) for each side.

Maximum Mouth Opening: Maximum assisted and unassisted mouth opening values (mm) were measured as the distance between lower and upper incisors.

Bimanual palpation of masticatory muscles and joint sensitivity: All patients in the study were assessed for pain by palpating the origin, belly, and insertion of the masseter, lateral pterygoid, medial pterygoid, digastric, sternocleidomastoid and trapezius muscles. The preauricular and endaural region of the TMJ was also evaluated on palpation. The degree of tension and pain in the muscles during palpation was reported by the patient using a scoring system. The patients expressed pain intensity according to the 0-3 point scale in the examination form of the RDC/TMD. According to this scale, scores were recorded as 0 (no pain), 1 (mild pain), 2 (moderate pain), or 3 (severe pain). The total pain score was attained by summing the pain scores from each muscle.

Sleep Quality: The patients were asked to grade their sleep quality before treatment and at 1 and 3 months after treatment using a Visual Analog Sleep Quality Scale ranging from 0 (poor sleep quality) to 10 (excellent sleep quality).

STATISTICAL ANALYSIS

The study data were analyzed using IBM-SPSS Statistics 22 (SPSS Inc., Chicago, IL) software package. The Shapiro-Wilk test was used to analyze the conformity of the data to normal distribution. In addition to descriptive statistical methods (mean, standard deviation, frequency). Normally distributed quantitative data were compared among groups using one-way ANOVA, and Tukey's honestly significant difference test was used to determine which group was responsible for the difference. Non-normally distributed parameters were compared between groups using the Kruskal-Wallis test, and the Mann-Whitney U test was used to identify the group responsible for the difference. Normally distributed variables were compared within groups using repeated-measures ANOVA (with post-hoc Bonferroni correction). While non-normally distributed data were compared using Friedman's test (with post-hoc Wilcoxon's signed-rank test). Qualitative data were compared using the chi-square test, Fisher's exact chi-square test, and Fisher-Freeman-Halton tests. Relationships between non-normally distributed parameters were evaluated with Spearman's rho correlation analysis. P value <0.05 was considered statistically significant. G*Power software package (Version 3.0.10, Franz Faul, Universität Kiel, German) was used for power analysis to determine the sample size for the study.

RESULTS

Following examination of 300 (224 females and 76 males) patients, 45 of them who met the inclusion criteria were included. The study population comprised 8 (17.8%) males and 37 (82.2%) females age ranging from 18 to 65 years. The mean age was 30.6±11.43 years.

Group 1 included 17 (13 female and 4 male) patients who were prescribed oral melatonin 6 mg once daily (Melatonina 3 mg tablet, Przedsiębiorstwo Farmaceutyczne LEK-AM Co. Ltd., Ostrzykowizna, Poland) to be taken 30 minutes before bed for 30 days. Group 2 included 12 patients (10 female and 2 male) who were prescribed tenoxicam 20 mg once daily (Tilcotil 20-mg tablets; Roche, İstanbul, Türkiye) for 30 days. Group 3 included 16 (14 female and 2 male) patients who were recommended with only BT, which involved a soft diet and modifying habits.

The distribution of patients by age, sex, and treatment groups is shown in Table 1. There was no statistically significant difference among the groups in terms of mean age or sex distribution (p>0.05). The group sample size was determined using power analysis where the effect size was 0.542 and the standard deviation was 0.73. With a significance criterion of α=0.05 and power=0.80, minimum sample size needed with this effect size was n=11.

FACIAL PAIN

Facial pain did not differ significantly between the groups before treatment (p>0.05). After 1 month of treatment, there was a statistically significant difference in facial pain among the groups (p=0.047). A significantly higher proportion of patients in the melatonin group reported no pain [n=10 (58.8%)] compared to those in the NSAID [n=1 (8.3%)] and BT [n=4 (25%)] groups (p=0.011 and p=0.044. respectively) (Table 2). There was no significant dif-

TABLE 1: Distribution of patients according to age, sex, and treatment group.

	Patient number	Males	Females	Age	
	n (%)	n (%)	n (%)	Minimum-Maximum	X̄±SD
Melatonin	17 (37.8)	4 (23.5)	13 (76.5)	20-50	33.35±9.51
NSAID	12 (26.7)	2 (16.7)	10 (83.3)	16-65	33.42±14.44
BT	16 (35.6)	2 (12.5)	14 (87.5)	16-62	26.62±10.34
Total	45 (100)*	8 (17.8)	37 (82.2)	16-65	30.6±11.43
		[1]0.705		[2]0.219	

[1]Chi-square test; [2]One-way ANOVA test; *p<0.05; SD: Standard deviation; NSAID: Non-steroid anti-inflammatory drug; BT: Behavioral therapy.

TABLE 2: Comparison of facial pain between the treatment groups before treatment and at 1 and 3 months after treatment.

Facial pain		Melatonin n (%)	NSAID n (%)	BT n (%)	p value
Before treatment	Right	0 (0)	1 (8.3)	3 (18.8)	[1]0.299
	Left	2 (11.8)	3 (25)	3 (18.8)	
	Both sides	15 (88.2)	8 (66.7)	10 (62.5)	
After treatment 1st month	No pain	10 (58.8)	1 (8.3)	4 (25)	[2]0.047*
	Right	0 (0)	3 (25)	4 (25)	
	Left	4 (23.5)	4 (33.3)	2 (12.5)	
	Both sides	3 (17.6)	4 (33.3)	6 (37.5)	
After treatment 3rd month	No pain	11 (64.7)	6 (50)	7 (43.8)	[2]0.336
	Right	1 (5.9)	2 (16.7)	5 (31.3)	
	Left	1 (5.9)	3 (25)	2 (12.5)	
	Both sides	4 (23.5)	1 (8.3)	2 (12.5)	

[1]Fisher's exact test; [2]Chi-square test; *p<0.05; NSAID: Non-steroid anti-inflammatory drug; BT: Behavioral therapy.

ference between the NSAID and BT groups (p>0.05). There was also a significant difference among the groups in terms of right-side facial pain after 1 month of treatment (p=0.046). Significantly more patients in the melatonin group reported the absence of pain on the right side [n=14 (82.4%)] compared to the NSAID [n=4 (33.3%)] group (p=0.009). No difference was detected between the other groups (p>0.05).

At 3 months there was no statistically significant difference in the prevalence of facial pain among the groups (p>0.05).

MAXIMUM MOUTH OPENING

Comparisons of mouth opening values before treatment and at 1- and 3-month follow-ups are shown in Table 3.

TABLE 3: Comparison of painless unassisted, maximum unassisted, and maximum assisted mouth opening distances in the treatment groups before treatment and at 1 and 3 months after treatment.

		Melatonin X̄±SD (median)	NSAID X̄±SD (median)	BT X̄±SD (median)	p value
Painless unassisted mouth opening (mm)	Bt-1st month difference	1.12±1.32 (1)	0.17±0.83 (0)	0.13±1.41 (0)	0.029*
	Bt-3rd month diffference	1.59±1.54 (1)	0.92±3.92 (0)	0.63±3.2 (1)	0.034*
Maximum unassisted mouth opening (mm)	Bt-1st month difference	3.06±2.73 (2)	1.83±4.06 (1)	1.5±2.97 (1)	0.044*
	Bt-3rd month difference	3.35±2.69 (3)	1.33±3.11 (1)	1.81±3.85 (1.5)	0.010*
Maximum assisted mouth opening (mm)	Bt-1st month difference	3.06±1.95 (3)	1.92±3.34 (1)	1.38±2.66 (0.5)	0.018*
	Bt-3rd month difference	3.59±2.06 (3)	-1.5±11.74 (1)	1.75±3.68 (1)	0.003*

Kruskal-Wallis test; *p<0.05; SD: Standard deviation; Bt: Before treatment; NSAID: Non-steroid anti-inflammatory drug; BT: Behavioral therapy.

TABLE 4: Comparison of sleep quality in the treatment groups before treatment and at 1 and 3 months after treatment.

Sleep quality scores	Melatonin X̄±SD (median)	NSAID X̄±SD (median)	BT X̄±SD (median)	p value
Bt-1st month difference	4.19±1.70 (4)	0.58±0.90 (0.5)	0.50±0.89 (0)	0.000*
Bt-3rd month difference	3.70±1.61 (4)	0.67±1.15 (0)	0.37±0.5 (0)	0.000*

Kruskal-Wallis test; *p<0.05; SD: Standard deviation; Bt: Before treatment; NSAID: Non-steroid anti-inflammatory drug; BT: Behavioral therapy.

Mean maximum painless unassisted mouth opening was significantly lower in the BT group than the melatonin and NSAID groups at both 1 month (p=0.000 and p=0.004. respectively) and 3 months (p=0.000 and p=0.004. respectively) while no significant differences were observed between the melatonin and NSAID groups.

The melatonin group had significantly greater maximum assisted mouth opening at 1 month and greater maximum unassisted mouth opening at 3 months compared to the BT group (p=0.026 and p=0.031. respectively).

The amount of increase in painless unassisted mouth opening after 1 month of treatment compared to pre-treatment values differed significantly among the groups (p=0.029). The melatonin group showed significantly greater increase when compared with the NSAID and BT groups (p=0.033 and p=0.021. respectively).

In terms of increase in maximum unassisted mouth opening at 1 month after treatment, the increase in the melatonin group was significantly greater than those seen in the NSAID and BT groups (p=0.037 and p=0.032. respectively). The melatonin group also showed significantly greater improvement in maximum unassisted mouth opening at 3 months after treatment compared to the NSAID group (p=0.001).

There was a statistically significant difference among the groups in the amount of increase in maximum assisted mouth opening at 1 and 3 months (p=0.018 and p=0.003 respectively). This was a significantly higher increase in the melatonin group compared to the NSAID group (p=0.013 and p=0.019. respectively) and BT group (p=0.003 and p=0.004. respectively).

PALPATION OF MASTICATORY MUSCLES PAIN

Compared to the BT group the melatonin group showed a significantly greater reduction in muscle pain scores upon palpation at 1 month after treatment compared to pre-treatment scores (p=0.005). There was no significant difference between the NSAID and melatonin groups (p>0.05). At 3 months, there was no statistically significant difference between the groups in terms of reduction in muscle pain scores upon palpation (p>0.05).

SLEEP QUALITY

Sleep quality score was significantly lower in the melatonin group compared to the NSAID and BT groups before treatment (p=0.002 and p=0.000. respectively), while there was no significant difference between the NSAID and BT groups (p>0.05). At 1 and 3 months after treatment. There was no statistically significant difference in sleep quality scores between the treatment groups (p>0.05).

The melatonin group showed significantly greater improvement in sleep quality scores at 1 and 3 months after treatment compared to the other two groups (p=0.000 for both) (Table 4).

When the correlation between sleep quality and muscle pain was evaluated, no significant correlation was detected among the groups at 1 and 3 months (p>0.05).

DISCUSSION

MP is a chronic condition that causes pain in the musculoskeletal system which is confined to a particular area. MP is the second most recurrent type of orofacial pain. Epidemiological studies have shown that 75% of the population has at least one symptom of TMJ disorders in the joint or masticatory muscles.

This condition is frequently associated with temporomandibular joint dysfunction, which comprises masticatory muscles, periauricular area and related structures. The pathophysiological mechanism of these disorders has not been fully elucidated.[2,15,16]

In this study, the diagnosis was made based on the RDC/TMD history-taking and examination protocol.[14] All of the 45 patients included in the study had presented MP. Because the etiological factors underlying MP are not well understood. The use of non-invasive and predictable conservative treatment options, including soft diet, physical therapy, BT, NSAIDs, antidepressants and occlusal splints are recommended.[3,17,18]

The inflammation and pain associated with TMJ disorders are generally difficult to tolerate. Even when mild despite numerous efforts, there is still not a definitive proposed treatment option for MP. NSAIDs are usually preferred for inflammation and inflammatory pain. Consequently, the jaw movement restriction associated with pain is also indirectly treated pharmacologically. Tenoxicam, meloxicam, and ibuprofen are NSAIDs that are often used and are effective for MP and inflammation.[19,20]

Tenoxicam, which is an oxicam derivative of NSAIDs, is a strong analgesic and anti-inflammatory agent with proven effectiveness in postoperative pain. Once-daily use is sufficient.[20] In this study, we evaluated the effect of tenoxicam because it is one of the most prescribed drugs for MP. Although often used in the treatment of TMJ disorders, the long-term use of these drugs can lead to severe adverse effects. NSAIDs are known to cause gastrointestinal damage that manifests with ulcers and inflammation, especially in the stomach and duodenum. Due to these side effects, the use of analgesic agents that have fewer side effects and can reduce NSAID use is of substantial clinical importance.[21,22]

The authors aimed to evaluate the anti-inflammatory and analgesic effect of melatonin in patients with MP and to compare its effectiveness with that of NSAIDs. Melatonin is an endogenous chronobiotic and antioxidant and its analgesic effect has been demonstrated in numerous experimental and clinical studies.[23,24] There have been reports on its effectiveness in reducing pain in cases of chronic pain such as fibromyalgia, irritable bowel syndrome, migraine, chronic back pain and tension headache.[25,26]

In a randomized study on fibromyalgia treatment, Citera et al. prescribed 3 mg melatonin orally 30 minutes before bed for 4 weeks in 21 female patients with fibromyalgia.[27] They reported a significant improvement in sleep quality and significant decrease in painful trigger points.

In a randomized study by de Zanette et al. 63 female fibromyalgia patients aged 18-65 were treated in 3 groups. Group 1 received 25 mg amitriptyline before bed for 6 months.[28] Group 2 received 10 mg melatonin, and Group 3 received both. The authors determined that the combined treatment and melatonin alone were more effective than amitriptyline for morning stiffness and sleep disorder.

In a double-blind, randomized study by Vidor et al. 32 women aged 20-40 years with TMJ disorder with MP received 5 mg oral melatonin before bed for 4 weeks and showed a 44% reduction in pain scores compared to patients who received placebo.[29] 39% increase in pressure-pain threshold and significant reduction in analgesic consumption. The authors stated that melatonin increased sleep quality but that its effect on pain was independent of its effect on sleep.

Consistent with the literature, we observed a decrease in MP in the present study, and it showed that melatonin had a better short-term analgesic effect than the other treatments. In previous studies demonstrating the positive analgesic effects of melatonin, oral melatonin was administered at doses of 3-10 mg, and no side effects were reported. However; experimental and clinical studies have offered no clear results regarding the optimal anti-nociceptive and analgesic dose of melatonin. Based on the scientific data, 5-20 mg melatonin can be taken orally or sublingually.[30,31]

A dose of 6 mg of oral melatonin was used in the present study, and no side effects were detected. Melatonin is reported in the literature as safe for short-term use, even at high doses. Mild side effects such as dizziness, headache, nausea, and sleepiness

were reported at rates comparable to those seen with placebo.[32,33]

At present, reports indicate that sleep bruxism is 70% due to pathophysiological factors, followed by lesser contributions from psychosocial and morphological factors. The sleep disorders included in these pathophysiological factors may be attributed to sleep physiology since bruxism is especially common during sleep.[34] Smith et al. found that the rate of insomnia was high in their study of 53 patients with myofascial TMJ disorder and suggested that primary insomnia is associated with hyperalgesia and clinical insomnia may play a pathophysiological role in TMJ disorder and other central sensitivity syndromes.[7] Serra-Negra et al. identified poor sleep quality as an important factor in dental students with nocturnal and daytime bruxism.[35] In the current study, no significant correlation was observed between total muscle pain scores upon palpation and sleep quality before or at 1 and 3 months after treatment.

Limitations of this study may be the small number of patients included in each group and the short-term follow-up period. Further studies with larger patient groups and long-term evaluation are recommended to compare different treatment modalities.

CONCLUSION

In this study, all treatment methods successfully improved the clinical symptoms in patients with MP. These results suggest that melatonin is more effective than the other two treatment options. In the short term, melatonin has an analgesic and anti-inflammatory effect independent of sleep quality, suggesting that melatonin may have nociceptive efficacy as an alternative to other NSAIDs.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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