

EFFECTIVENESS OF MELATONIN USE IN TREATMENT OF PREMATURE EJACULATION COMBINED WITH ERECTILE DYSFUNCTION

© A.V. Kuzmenko, T.A. Gyaurgiev, A.A. Vishnyakov, D.V. Tizyo

N.N. Burdenko Voronezh State Medical University of the Ministry of Healthcare of the Russian Federation, Voronezh, Russia

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⊗ The article presents the results of the treatment of 60 patients with premature ejaculation in combination with erectile dysfunction. Patients were divided into three groups, in which patients were prescribed non-drug treatment, or sildenafil 50 mg on demand, or sildenafil 50 mg on demand in combination with melatonin 3 mg at night. Duration of treatment was 6 months. The psychoemotional status, quality of life, quality and duration of intercourse, erectile function and chrono-rhythms of patients were assessed. The results of the study showed that treatment with sildenafil in combination with melatonin was the most clinically effective, which manifested in prolongation of sexual intercourse, improvement of the quality of erection and normalization of the chronobiological status of patients.

⊗ **Keywords:** premature ejaculation; erectile dysfunction; melatonin; sildenafil; chronorhythms; desynchronosis.

ЭФФЕКТИВНОСТЬ ПРИМЕНЕНИЯ МЕЛАТОНИНА В ЛЕЧЕНИИ ПРЕЖДЕВРЕМЕННОЙ ЭЯКУЛЯЦИИ, СОЧЕТАННОЙ С ЭРЕКТИЛЬНОЙ ДИСФУНКЦИЕЙ

© А.В. Кузьменко, Т.А. Гяургиев, А.А. Вишняков, Д.В. Тызьо

Федеральное государственное бюджетное образовательное учреждение высшего образования «Воронежский государственный медицинский университет им. Н.Н. Бурденко» Министерства здравоохранения Российской Федерации, Воронеж

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⊗ В статье приведены результаты лечения 60 пациентов с преждевременной эякуляцией в сочетании с эректильной дисфункцией. Пациенты были разделены на 3 группы, в которых больным назначали немедикаментозное лечение, или силденафил в дозе 50 мг по требованию, или силденафил в дозе 50 мг по требованию в сочетании с мелатонином в дозе 3 мг ежедневно на ночь. Продолжительность лечения 6 мес. Произведена оценка психоэмоционального статуса, качества жизни, качества и продолжительности полового акта, эректильной функции и хроноритмов пациентов. Результаты исследования показали, что лечение силденафилом в сочетании с мелатонином оказалось наиболее клинически эффективным, что проявлялось в пролонгировании полового акта, улучшении качества эрекции, а также нормализации хронобиологического статуса пациентов.

⊗ **Ключевые слова:** преждевременная эякуляция; эректильная дисфункция; мелатонин; силденафил; хроноритмы; десинхроноз.

INTRODUCTION

According to the definition of the International Society for Sexual Medicine, premature ejaculation (PE) is an impairment of the male sexual func-

tion characterized by ejaculation that occurs before or within 1 min after vaginal penetration, the inability to delay ejaculation, and the presence of psychological stress [1]. PE is one of the urgent problems

in urology, which has both a medical and social significance. The prevalence of this copulatory disorder among the male population of the Russian Federation is 27.7% [2].

There are two types of PE: primary and secondary. The patient's inability to control ejaculation from the onset of sexual activity is classified as primary PE. The etiological factors in the development of primary PE include hypersensitivity of the glans penis, short frenulum, and excessive excitability of the corresponding parts of the brain [3–5]. Currently, the neurobiological theory is the most popular theory of the onset of this disorder. According to this theory, PE occurs as a result of dysregulatory processes in the brain serotonergic system [6]. This concept is confirmed by the successful use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of PE [7, 8]. Secondary PE is an acquired form of the disorder, which develops in the presence of chronic prostatitis, erectile dysfunction, and hyperthyroidism [9–11]. There is also evidence that secondary PE develops in the presence of cerebral disorders [12].

The combination of PE and erectile dysfunction, which significantly worsens the quality of a man's sexual life, is of great clinical importance. It should be noted that the causal relationship between these two conditions is still to be clarified. Sometimes, in case of PE due to psychological discomfort and the fear of anticipating failure, psychogenic erectile dysfunction occurs, while in other situations, due to unstable erection, the patient develops a desire for intercourse, which ultimately leads to PE [13].

In the treatment of PE patients, behavioral therapy (the “start-stop” technique, the “compression” method) and pharmacotherapy are used, as well as surgical interventions aimed at denervation of the penis [14]. The method of choice is pharmacotherapy using SSRIs, which are third generation antidepressants [7, 8, 15]. However, due to the fact that this group of drugs has side effects in the form of decreased libido and erectile function [16], their use in case of PE combined with erectile dysfunction is limited. Phosphodiesterase inhibitors type 5 (PDE5 inhibitors), which are actively used in the treatment of erectile dysfunction and urinary disorders [17, 18], have also shown positive results when used in the treatment of PE [10]. It is believed that the mechanism of the therapeutic effect of PDE5 inhibitors in PE patients involves the compression of the

nerve bundles of the dorsal nerve of the penis, which results in a decrease in the sensitivity of the glans penis [19]. Nevertheless, some studies indicate the ineffectiveness of PDE5 inhibitors in this group of patients [20].

The results of several studies show that the use of melatonin through a cascade of biochemical reactions involving the CYP2D subtype of the polymorphic cytochrome p-450 increases the concentration of endogenous serotonin in the brain [21, 22]. Melatonin is a hormone involved in the chronobiological processes of the body, has a rhythmic and circadian nature, with a key clinical significance [23–25]. There are no data on melatonin efficiency in the treatment of PE.

This study aimed to evaluate the efficiency of using of PDE5 inhibitors in combination with melatonin for the treatment of PE patients with erectile dysfunction.

MATERIALS AND METHODS

A total of 60 male patients aged 20–50 years with PE in combination with erectile dysfunction were examined. Based on five positive responses in the Premature Ejaculation Criteria (PEC) questionnaire and a period of intravaginal delay in ejaculation of 1 min or less, the diagnosis of PE was confirmed. Patients measured this indicator independently using a stopwatch. Erectile dysfunction was diagnosed with a score of 20 or less according to the International Index of Erectile Function-5 (IIEF-5) questionnaire.

The inclusion criteria for the study were as follows: presence of a permanent sexual partner, period of intravaginal delay of ejaculation for 1 min or less, presence of 5 positive responses in the PEC questionnaire, 20 or less points on the IIEF-5 questionnaire, less than 13 points on the Hamilton Rating Scale for Depression (HDRS), less than 10 points on the Hospital Anxiety and Depression Scale, and decreased physical and mental quality of life according to the SF-36 (Short Form-36) questionnaire.

The exclusion criteria for the study were chronic prostatitis, hyperthyroidism, androgen deficiency, diseases of the cardiovascular system (atherosclerosis, ischemic heart disease), diabetes mellitus, and lesions of the central nervous system.

The patients were distributed into three groups of 20 persons each using the random sampling method: the comparison group (CG),

treatment group 1 (TG-1), and treatment group 2 (TG-2). Diet, sports, enrichment of the diet with biologically active additives, and behavioral therapy ("start-stop" technique, "compression" method) were prescribed to the CG patients. PDE5 inhibitor sildenafil at a dose of 50 mg on demand was prescribed to the TG-1 patients, and TG-2 patients received a similar dose of sildenafil and melatonin at a dose of 3 mg 30–40 mins before bedtime. Treatment duration was 6 months.

Throughout this study, patients were examined three times, namely; before the start of treatment (visit 1), three months (visit 2), and six months (visit 3) after the start of therapy. It included the determination of the patient's psychoemotional state using the HARS and HDRS scales, as well as PEC and SF-36 questionnaires, and an assessment of the chronobiological status, during which signs of desynchronization were detected. In addition, each patient kept a diary of sexual activity throughout the treatment period.

RESULTS

During the examination at visit 1, before the start of treatment, the majority of patients had decreased total score on the HDRS and HARS questionnaires, which corresponded to a change in the psychoemotional state in the form of mild depression and subclinical anxiety. In addition, according to the results of the analysis of the SF-36 questionnaires filled out by patients, all patients had a decrease in the quality of life. Mild-to-moderate erectile dysfunction,

according to the FIEF-5 scale, as well as premature ejaculation, based on the PECK questionnaire, was also diagnosed in all patients (Table 1).

Signs of desynchronizes were recorded in all groups while the graph of chronogram curves was analyzed. In the CG, the curves were located in zone 3 in 15 (75%) patients and in zone 2 in 5 (25%) patients. In TG-1, the number of patients with chronorhythm curves in zone 3 was 17 (85%) and 3 (5%) in the zone 2. In TG-2, there were 16 (80%) patients with chronorhythm curves in zone 3, and 4 (20%) patients with chronorhythm curves in zone 2.

At the visit 2, that is, after three months of treatment, a significant improvement in the psychoemotional status, as well as the quality of life of patients was recorded in TG-1 and TG-2 patients (Table 1). Evaluation of the results of the diary of sexual activity demonstrated the presence of positive dynamics in the CG in 7 (35%) patients, and in 7 (35%) and 8 (40%) patients of the TG-1 and TG-2, respectively. The analysis of the graphs of chronograms revealed normalization of the chronobiological rhythms, whose curves were located in zone 1, in 2 patients of the CG. Moreover, the curves were recorded in 8 (40%) patients in the zone 2, and in 10 (50%) patients in the zone 3. The study of the TG-1 results showed that the chronograms were recorded in 8 (40%) patients in the zone 1, in 7 (35%) patients in the zone 2, and in 5 (25%) patients in the zone 3. In TG-2, desynchronization was absent in 12 (60%) patients, the curves were located in zones 2 and 3 in 6 (30%) and 2 (10%) patients, respectively.

Results of examination of patients of three study groups during treatment ($n = 60$)

Результаты обследования пациентов трех групп исследования в процессе лечения ($n = 60$)

Examination method	Comparison group ($n = 20$)			Treatment group 1 ($n = 20$)			Treatment group 2 ($n = 20$)		
	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
HDRS, points	10.1 ± 0.49	9.0 ± 0.38 *	7.0 ± 0.35 *	10.5 ± 0.52 #	9.0 ± 0.45 *#	7.0 ± 0.15 *#	11.2 ± 0.56 ##	8.2 ± 0.43 *##	6.8 ± 0.34 *##
HARS, points	9.9 ± 0.45	8.5 ± 0.42 *	6.7 ± 0.3 *	9.5 ± 0.47 #	8.1 ± 0.43 *#	6.8 ± 0.25 *#	10.1 ± 0.45 ##	7.9 ± 0.4 *##	6.6 ± 0.3 *##
SF 36, %	100	65 *	0 *	100 #	60 *#	0 *#	100 ##	50 *##	0 *##
IIEF 5, points	16.7 ± 0.83	17.1 ± 0.85 *	19.1 ± 0.75 *	15.1 ± 0.75 #	18.5 ± 0.92 *#	21.1 ± 0.5 *#	15.9 ± 0.79 ##	19.2 ± 0.9 *##	21 ± 0.3 *##
PEC, %	100	75 *	5 *	100 #	50 *#	0 *#	100 ##	40 *##	0 *##

* Significance of the differences in the results of the previous visit in this group $p < 0.05$; # significance of the differences with the comparison group $p < 0.05$; ## significance of differences with the comparison group and control group 1 $p < 0.05$.

During the examination after six months (visit 3), the results of the questionnaire survey of patients by HDRS, HARS, SF-36, as well as PEC were within normal limits (Table). At the same time, the mean score in the CG patients on the IIEF-5 scale was 19.1 ± 0.75 , which is interpreted as mild erectile dysfunction. In patients of both treatment groups, the examination results using the above questionnaires were within the normal range. According to the results of the analysis of the data of the diary of sexual activity, positive dynamics was noted in 80% of CG patients compared with 35% at visit 2, 90% in TG-1 patients compared to 35% at visit 2, and 95% in TG-2 patients compared to 40% at visit 2. Desynchronization was absent in 12 (60%) CG patients, while in the rest, the curves were located in zone 2, when the chronorhythms were been registered. In TG-1, normal chronorhythms were found in 18 (90%) patients, and in 2 (10%) patients, the curves were located in zone 2. In TG-2, desynchronization was absent in all patients (100%).

DISCUSSION

Analysis of the data obtained during the study enabled to emphasize the following most important results.

During the examination, in all patients in all study groups, changes in the psychoemotional state and a decrease in the quality of life were noted. During the therapy, these parameters improved, with the most pronounced positive result noted in TG-2, where the average score on the HDRS and HARS scales after six months was 6.8 ± 0.34 and 6.6 ± 0.3 with the initial being 11.2 ± 0.56 and 10.1 ± 0.45 , respectively. With regard to erectile function, in TG-1 and TG-2 at visit 3, a decrease in the severity of erectile dysfunction was recorded. Average score on the IIEF-5 scale in the CG after six months of treatment was 19.1 ± 0.75 , which was interpreted as moderate erectile dysfunction. In addition, PE symptoms were noted in 5% of patients in this group. The positive therapeutic effect of melatonin, registered in the course of the study was presumably associated with an increase in serotonin levels in the corresponding parts of the brain, which was confirmed by the data of A. Haduch et al. [22] on an increase in the presynaptic pool of serotonin vesicles due to a chain of biochemical reactions involving the CYP2D subtype of cytochrome p-450 of brain neurons. As a result, the concentration of serotonin in

the synaptic cleft increases without inhibition of the receptors involved in the neurotransmitter reuptake. This aspect demonstrates fundamental differences in the mechanism of action of melatonin and the currently used SSRIs for the treatment of PE. Also, in all TG-2 patients after six months, normalization of chronorhythms was noted, which confirms the results of a number of studies indicating the leveling of the desynchronization conditions during the therapy for the underlying disease [24, 25].

CONCLUSION

Thus, all PE patients had signs of subclinical anxiety, mild depression, decreased quality of life, and mild-to-moderate erectile dysfunction. In addition, desynchronization was detected in all patients under study. The use of melatonin at a dosage of 3 mg per day before bedtime, together with PDE5 inhibitors, demonstrated a positive result in the correction of PE, and also eliminated depression and anxiety, and normalized the erection and quality of life. Melatonin also corrected the chronobiological status of patients. Nevertheless, the data obtained require confirmation in further scientific studies with a larger number of cases.

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Information about the authors:

Andrey V. Kuzmenko — Doctor of Medical Science, Professor, Head of the Department. N.N. Burdenko Voronezh State Medical University of the Ministry of Healthcare of the Russian Federation, Voronezh, Russia. E-mail: kuzmenkoav09@yandex.ru.

Timur A. Gyaurgiev — Candidate of Medical Science, Associate Professor, Department of Urology. N.N. Burdenko Voronezh State Medical University of the Ministry of Healthcare of the Russian Federation, Voronezh, Russia. E-mail: tima001100@mail.ru.

Artem A. Vishnyakov — Consultant, Department of Urology. N.N. Burdenko Voronezh State Medical University of the Ministry of Healthcare of the Russian Federation, Voronezh, Russia. E-mail: bars0505@mail.ru.

Daler V. Tizyo — Student. N.N. Burdenko Voronezh State Medical University of the Ministry of Healthcare of the Russian Federation, Voronezh, Russia. E-mail: tyzo.daler@mail.ru.

Сведения об авторах:

Андрей Владимирович Кузьменко — д-р мед. наук, заведующий кафедрой урологии. ФГБОУ ВО ВГМУ им. Н.Н. Бурденко Минздрава России, Воронеж. E-mail: kuzmenkoav09@yandex.ru.

Тимур Асланбекович Гяургиев — канд. мед. наук, доцент кафедры урологии. ФГБОУ ВО ВГМУ им. Н.Н. Бурденко Минздрава России, Воронеж. E-mail: tima001100@mail.ru.

Артем Андреевич Вишняков — консультант кафедры урологии. ФГБОУ ВО ВГМУ им. Н.Н. Бурденко Минздрава России, Воронеж. E-mail: bars0505@mail.ru.

Далер Валерьевич Тызьо — студент. ФГБОУ ВО ВГМУ им. Н.Н. Бурденко Минздрава России, Воронеж. E-mail: tyzo.daler@mail.ru.