THE EFFECTIVENESS OF MELATONIN IN THE COMPLEX TREATMENT OF HYPERTENSION IN PATIENTS WITH STAGE 5 CHRONIC KIDNEY DISEASE

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The problem of effective treatment of a patient with high cardiovascular risk is a complex task of modern medicine. Mortality from cardiovascular disease takes first place among the causes of mortality and disability worldwide, in spite of medical level. Recently, there has been a progressive increase in the number of patients with chronic kidney disease (CKD), the risk of mortality in which is much higher than in patients of the general population due to a combination of cardiovascular risk factors (hypertension, proteinuria, decrease in glomerular filtration rate, hyperuricemia, cardiac remodeling, and cardiac remodeling, etc. [23]. Arterial hypertension (AH) as a cause of fatal cardiovascular events is compared with a noninfectious epidemic, more and more often becomes resistant to AH, and its prevalence of CKD is in 2-3 times higher than in the general population [24,29].

In patients with terminal renal insufficiency, prior to initiation of renal replacement therapy, hypertension exceeds 90%. There is a close connection between hypertension and CKD: on the one hand, the development and progression of CKD lead to increased of arterial hypertension (BP), on the other hand, the presence of hypertension is associated with a significant deterioration in the prognosis of patients with CKD. Therefore, the search for new approaches to optimize the treatment of hypertension in patients with CKD by studying all possible pathogenetic mechanisms of hypertension is an urgent task today [15].

AH in a patient with CKD is a multifactorial condition in which the pathogenesis plays by the violation of the dynamic equilibrium between the pressor and depressor mechanisms of neurohumoral regulation of cardiovascular system activity in general and the regulation of blood pressure [4,8,16]. A special place in the complex system of mechanisms of neurohumoral regulation of blood pressure belongs to melatonin, which reduces the activity of the pressor mechanisms of neuroendocrine regulation, regulates the tone of blood vessels through specific M-receptors of the endothelium, limits the vasoconstrictor effects of noradrenaline, vasopressin, endothelin-I and other biologically active substances, improves the state of baroreflex regulation and exhibits powerful antioxidant properties [11].

It is well-known that in physiological conditions the secretion of melatonin by neuroendocrine epiphysis cells occurs mainly at night during sleep, coinciding with the physiological nocturnal decrease of blood pressure [2,3,17]. A number of studies show that with insufficient production of melatonin, the activation of the renin-angiotensin-aldosterone system (RAAS) occurs, decreases baroreflex activity, increases platelet aggregative ability, decreases fibrinolytic activity of the blood, increases vascular tone, which contributes to the adverse daily profile of blood pressure and the development of cardiovascular complications [5,6,9,10,25]. Unfavorable daily profiles of blood pressure (non-dipper or night-picker) are manifestations of circadian rhythm disturbances in the body due to serum melatonin deficiency, vegetative dysfunction, RAAS hyperactivity, sodium-dependent mechanism of hypertension, hyperuricemia on various multiorgan messages in CKD [7,18,26].

The time index (TI) of hypertension (a period of elevated BP during the day) has been suggested by some authors for predicting the risk of cardiovascular events in patients [30]. An independent predictive value of the value of pressure load regarding to the development of myocardial remodeling has been established. The speed of the morning rise (SMR)in blood pressure is important indicator, as it is known that the morning period is considered to be a time of cardiovascular catastrophes [32-34]. This is due to the physiological activation of sympatho-adrenal and renin angiotensin aldosterone system (RAAS), which leads to increased vascular tone, decreased fibrinolytic properties of blood with the development of myocardial infarction, stroke in the morning, so the speed of the morning rise (SMR) in blood pressure in the period from 4:00 to 10:00 a.m. is considered as a starting mechanism for the development of complications [20].

Nocturnal hypertension is a risk factor for cardiovascular events, but its causes have not been fully learned. Insufficient reduction (less than 10%) or increase in blood pressure at night (adverse daily blood pressure profile) is associated with a higher risk of cardiovascular events. There are excessive activation of sympatho-adrenal and RAAS, increasing the aggregation capacity of platelets, decreases fibrinolytic activity of the blood, increases vascular tone, which contributes to the development of cardiovascular complications in such patients at night and early in the morning on the background of insufficient production of melatonin by the epiphysis and low concentration of hormones in the blood [19,21,22].

It is believed that changes in blood pressure at night are more important and informative in predicting the development of cardiovascular complications than blood pressure in the daytime [27]. It was found that with an increase of systolic blood pressure (SBP) at night to 10 mm Hg. mortality risk increased to 21% [31] during conduction of the Dublin Outcome Study. In the analysis of the degree of nocturnal decrease in blood pressure and the nature of the distribution of the diurnal profile, it was found that the patients of the control group were characterized by half the number of people with physiological distribution of the BP and a moderate increase of people with unfavorable types of diurnal profile. The non-prognostic types of diurnal profile are : non-dipper and night-peakers, because insufficient reduction of blood pressure in the night period is associated with a high incidence of stroke, more frequent development of left ventricular myocardial hypertrophy [4,13,14].

There is no consensus on targeted blodd pressure and clear recommendations for the correction of hypertension in patients undergoing hemodialysis, with the exception of some ERA-EDTA and ESH-2017 reconciliation documents [28]. In addition, in dialysis patients with hypertension, the variability of blood pressure and the relationship with blood melatonin levels have not been studied sufficiently.

Objective - to study the efficacy of melatonin in the complex treatment of hypertension of patients with CKD of 5 stage with disruption of melatonin-forming function of the epiphysis (MFE).

Material and methods. The study included 60 patients of CKD at 5 stage: men - 25, women - 35, who were treated at the Kyiv Center of Nephrology and Dialysis, who had hypertension and MFE disorders.

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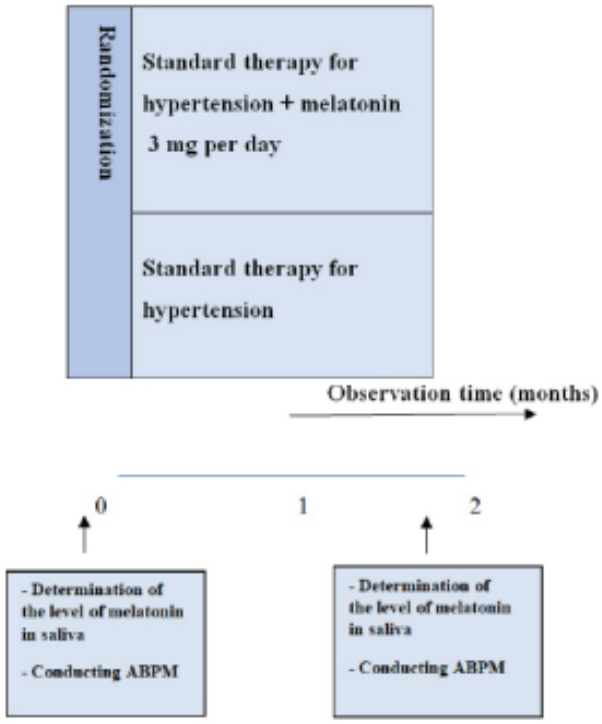
Research design is presented on Pic. 1.



Pic. 1. Research design

The characteristics of the surveyed groups are presented in Table 1.

Patients received chronic program hemodialysis 3 times a week on a continuous basis, which was 12 h/week. The duration of the dialysis session was 240 minutes; blood flow rate — 319±38 ml/min, with using bicarbonate dialysis solution. Kt/v ranged from 1,2 to 1,85. In all patients vascular access was presented by an arterio-venous fistula. The flow rate of the dialysis solution was 500 ml/min. Interdialysis weight gain was 3,3±0,3% of dry weight. The level of sodium in the dialysis solution was installed according to the level of sodium in the blood in the range 136-140 mmol/l.

Office BP measurements were performed before, during and after the hemodialysis session with the analysis of systolic BP, diastolic BP, pulse BP.

Ambulatory Blood Pressure Monitoring (ABPM) was performed during the day in dialysis period using the portable BP monitor system ABPM-04, Meditech (Hungary) after pre-briefing the patient in normal physical activity with continuous automatic BP measurement every 15 min daily and every 30 min at night.

The following indicators were analysed: average values of systolic and diastolic blood pressure of day, night, and all day, mean heart rate (HR) of day and night, circadian index (CI) of heart rate, blood pressure variability for daytime and sleep periods, degree of nocturnal decrease in blood pressure. The daily profile of BP was evaluated by the degree of nocturnal decrease of the systolic BP and the diastolic BP with using the commonly used criteria for determining the two-phase rhythm [12].

Measurement index and time index were considered for the study of high BP load indices. The daily rhythm of BP was evaluated on the basis of the determination of nocturnal BP decrease or the daily index (DI) of BP. DI of BP was calculated as the difference between the average values of BP during the periods of wakefulness and sleep.

We used the speed of the morning rise (SMR) in BP to characterize the morning dynamics of the BP, separately for systolic and diastolic BP (RMR BPs and RMR BPd).

A characteristic of the daily profile of BP was conducted according to the degree of reduction of systolic BP (SBP) at night. So patients with sufficient reduction (by 10-20%) were classified as dippers, with insufficient reduction (<10%) - non-dippers, and over-dipper - with excessive reduction (>20%), with nocturnal hypertension - night-peakers .

Verification of the diagnosis, determination of stage and degree of hypertension were performed according to the recommended criteria of 2018 by the European Society for the study of hypertension (ESH) / European Society of Cardiologists (ESC) [1].

Exclusion criteria: Alcohol addiction; excessive consumption of drinks with caffeine (equivalent to>3 cups of coffee per day); use of non-steroidal anti-inflammatory drugs; malignant neoplasms; obesity; treatment with hemodialysis sessions less than 3 times a week (less than 12 hours); Kt/V<1.2; mental disorders; concomitant pathology: endocrinological diseases, rheumatological diseases, myocardial infarction, acute damage of cerebral circulation; severe anemia.

The concentration of melatonin was determined by immunosorbent method with using a commercial set: Human MS (Melatonin Sulfate) ELISA Kit, Elabscience. Capture was conducted in the daytime at 16:00 and night time from 2:00 to 4:00, with a minimum lighting of 30 lx. Non-stimulated saliva was used, which was collected into capsule like Eppendorf in a volume of 1 ml, which was immediately frozen and stored at -20 ° C. The reference value of melatonin in saliva during the day was <4.9 pg/ml, and at night 52.3-149 pg/ml. Patients in the main group received standard 3 mg of melatonin for standard antihypertensive therapy, which was taken once daily at 22:00.

Table 1. Clinical and laboratory characteristics of the examined persons

Indicator	Main group, n=30	Comparison group, n=30
Men, people,%	12 (40,0%)	13 (43,0%)
Women, people,%	18 (60,0%)	17 (57,0%)
Age, years	48,4±11,6	50,5±17,2
Duration of hypertension, years	9,3±3,09	8,08±2,88
Dialysis experience, months	101,25±58,12	105,77±54,3
Body mass index, kg/m^2	23,7±4,8	23, 8±4,1
Albumin, g/l	41,5±4,2	40,2±3,6
Total cholesterol, mmol/l	5,0±0,9	5,2±1,3
Hemoglobin, g/l	99,8±18,4	101,8±19,0

Statistical analysis of the obtained data was performed by using Statistica SPSS 12.0 for Windows. In the normal distribution, the data are presented as average ± standard deviation, in other cases - as the median [25-75 percentiles]. Pearson's correlation coefficient was used to assess the significance of intergroup differences. P is assumed to be 0.05 considering testing of hypotheses for the critical level of significance. Spearman's rank correlation was used to assess the degree of correlation of quantitative traits. The study was conducted in accordance with the principles of bioethics.

Results and discussion. The patients of the main and control group were similarly compared by age, sex, disease experience, standard dialysis and antihypertensive therapy, violation of MFE.

Analyzing the incidence of MFE disorders in patients with stage 5 CKD treated with GD and practically healthy individuals, it draws attention to significantly lower rates of MT, both in the daytime and at night in patients. Thus, in patients with terminal renal failure compared with the control group, the level of MT in the daytime was lower by 52,4% (p<0,001), and more significantly in the night period by 82,6% (p<0,001).

In conducting ABPM in the examined patients, the average night and day indicators of SBP, DBP, time index, pressure variability significantly exceeded the normal values, which are presented in Table 2.

Patients of both groups can be attributed to Non-dipper according to the daily index of SBP and DBP, their number was 90% and the group "Night-peakers" was 10% of pa-

Table 2. ABPM indicators in the surveyed groups at the start of the study

Indicators	The main group, n=30	Comparison group, n=30	norm
Daytime			
Average SBP (mmHg)	174±19,94	172±18,73	100-135
Average DBP (mmHg)	91,54±1,619	92,51±1,917	60-85
TI SBP (%)	90 [60-90]	90 [60 -90]	<15
TI DBP (%)	80 [50-80]	80 [50 -80]	<15
Variability of SBP (mm Hg)	18	17	<15
Variability of DBP (mm Hg)	13	12	<15
Night time			
Average SBP (mmHg)	183±15,46	180±14,96	85-120
Average DBP (mmHg)	104,3±4,6	99±4,83	48-70
TI SBP (%)	100 [100 -100]	100 [100 -100]	<15
TI DBP (%)	100 [70 -100]	100 [70 -100]	<15
Variability of SBP (mm Hg)	20	19	<14
Variability of DBP (mm Hg)	16	15	<12
Morning dynamics			
SMR of SBP (mmHg)	25,7±10,8	22,9±11,3	<10
SMR ofDBP (mmHg)	13,8 ±2,6	12,9±1,7	<6

Table 3. ABPM indicators after 8 weeks of observation

Indicators	The main group, n=30	Comparison group, n=30
	After treatment	After treatment
Daytime		
Average SBP (mmHg)	152±17,48	168±17,35*
Average DBP (mmHg)	81±4,3	83,42±1,83
TI SBP (%)	80 [50 - 80]	85 [60 -90]
TI DBP (%)	70 [50 - 70]	70 [50 - 80]
Variability of SBP (mm Hg)	16	17
Variability of DBP (mm Hg)	11	12
Night time		
Average SBP (mmHg)	154±12,3	170±12,34*
Average DBP (mmHg)	97±3,8	95±2,8*
TI SBP (%)	80 [70 - 90]	92 [100 - 100]
TI DBP (%)	70 [50 -70]	85 [70 - 90]
Variability of SBP (mm Hg)	15	19
Variability of DBP (mm Hg)	12	15

*notes: * - statistical significance of differences in comparing with patients of the main group (p<0,05)*

tients. The time index of SBP and DBP at night is significantly increased, which indicates the stable nature of BP at night and is not a transitory phenomenon.

The speed of the morning rise (SMR) by SBP in the main group was 25,7±10,8 mmHg/h, by DBP – 13,8±2,6 mm Hg/h. The SMR in the comparison group was 22,9±11,3 mmHg/h by SBP, and 12,9±1,7 mmHg/h by DBP. Normal limits are significantly exceeded according to the obtained results of SMR and the SBP and the DBP. SMR of SBP and SMR of DBP exceeded the normal values in 2,5 times in the main group and in 2,3 times in the comparison group.

It was found that all high-pressure load values exceed the normal values during daytime, nighttime and in the daytime as a whole according to the results of the ABPM of the examined patients. All measurements of blood pressure during the analysis exceed the target values.

Analysis of hemodynamic parameters on the background of 2-month melatonin treatment and standard therapy revealed a decrease in the average levels of SBP and DBP, which is presented in Table 3.

Variability thresholds of SBP and DBP were recorded, with a statistically significant difference between SBP groups at night ($p<0,05$) in the analysis of treatment results in the main group. Patients receiving melatonin were characterized by significantly ($p<0,05$) lower variability of SBP and DBP.

A significant ($p<0,05$) decrease of average daily systolic blood pressure (SBP) by 12% is noted in patients of the main group , and average night systolic blood pressure (SBP) by 16% in comparative analysis of SBP in the dynamics on the background of treatment in both groups of patients. These indicators were 0.6% and 5.6% in the comparison group accordingly.The average daily diastolic blood pressure (DBP) decreased by 11.5% in the main group, compared in the comparison group by 5,6%. The average night diastolic blood pressure (DBP) decreased by 7% in the main group.

A decrease was noted in the patients of the main group ($p<0,05$) by 11% and 12,5%, in the comparison group these indicators decreased by 5% and 12%, respectively, when analyzing the TI of average daily SBP and average daily DBP indicators during the observation period. The decrease of TI during the night period was more pronounced. The average night SBP decreased by 20% in the main group and the average night DBP decreased by 30%. There was only a decrease in the average night DBP by 10% in the comparison group.

The study found that patients in the comparison group had the speed of the morning rise (SMR) of BP in 2,1 times increased compared to the main group of patients.

There is a clear positive effect of combination therapy with melatonin on the daily average and night average decrease of SBP and DBP when compared with the previous achieved level against the background of previously received antihypertensive therapy.

A statistically significant person's growth with dipper daily profile was observed from 14,3% to 44,5% in the overall structure ($p<0,05\%$) on the background of 8 weeks complex therapy

Table 4. Changes in antihypertensive therapy during the study

Number of antihypertensive drugs	At the beginning of the study		After 2 months		P
	Number of patients		Number of patients		
	Main group	Comparison group	Main group	Comparison group	
0	0	0	0	0	p<0,05
1	0	0	0	0	p<0,05
2	2 (6,7%)	1 (3%)	13 (43%)	1 (3%)	p<0,05
3	20 (66,6%)	21 (70%)	14(47%)	21(70%)	p<0,05
4	8 (26,7%)	8 (27%)	3 (10%)	8(27%)	p<0,05
Distribution in general					
Pharmacological group preparations					
ARBs	16	14	15	14	p<0,05
ACE inhibitors	2	6	0	6	p<0,05
CCB	38	29	32	38	p<0,05
Central action	38	29	33	39	p<0,05
Distribution in general					
The total number of prescriptions	94	97	79	97	p<0,05
For 1 patient	3,1	3,2	2,6	3,2	p<0,05

ARBs II – Angiotensin II receptor blockers; ACEinhibitors – angiotensin-converting-enzyme inhibitors; CCB – Calcium channel blockers

Table 5. The level of melatonin in saliva after treatment

Time of day	The main group (n=30)		Comparison group (n=30)		Reference values pg/ml
	Before treatment	After treatment	Before treatment	After treatment	
Daytime (pg/ml)	2,8±1.2	2,7±0,4	3,1±0,3	3,1±0,6*	<4,9
Night time (pg/ml)	20,2±3,7	57,4±1,5	21,5±3,9	22,3±3,7*	52,3-149,4

*notes: * - the statistical significance of differences compared to patients in the main group ($p<0,05$)*

with the addition of melatonin. On the contrary the proportion of patients with a non-dipper profile decreased from 44,5% to 27,6%, as the proportion of patients with a daily profile of night-peakear BP - from 22,4% to 4,8% (p<0,05%). There is no statistically significant changes in the structure of nocturnal decrease of BP in the comparison group.

Changes in the composition and amount of antihypertensive therapy, which were revealed during the study are presented in Table 4.

Improving the daily profile and reducing BP was observed in patients of the main group during the study because of the addition of melatonin to standard therapy, which indicating a close relationship of the hormone with circadian rhythms and its effect on hypertension.

Conclusions.

1. Patients with terminal renal failure have the low levels of MT compared to healthy subjects - in the daytime was lower by 52,4% (p<0,001), and more significantly in the night period by 82,6% (p<0,001).
2. According to ABPM, patients with CKD of 5 stage were characterized by pathological changes in circadian rhythm in the form of inadequate reduction of SBP and DBP in the night hours, which has manifestations in the form of a predominance of non-dipper profile types in the overall structure of patients by reducing the number of persons with a dipper profile. The was 90% of patients with a non-dipper profile and 10% of night-peakear. TI of hypertension in patients on hemodialysis significantly exceeded the allowable limits. Thus, TI of SBP exceeded the normal indicator by 75%, TI of DBP by 65% in the daytime. The TI of SBP and TI of DBP exceeded the allowable values by 85% at night. The speed of the morning rise of SBP and DBP exceeded almost twice the reference value.
3. The changes in the degree of nocturnal decrease of BP are paying attention assessing the dynamics of the daily profile of BP on the background of treatment. Thus, the number of patients in the «non-dipper» main group decreased from 44,5% to 27,6% (p<0,05%), like the proportion of patients with the «night-peakear» daily profile from 22,4% to 4,8% (p<0,05%). Besides, a statistically significant person's growth with dipper daily profile of BP was observed by 30,2% on the background of addition of melatonin to the antihypertensive therapy.
4. Against the background of complex treatment, there was a decrease in the patient's need for the dose and amount of antihypertensive drugs to achieve BP targets.
5. Melatonin was well tolerated in the complex treatment of hypertension in patients with CKD of 5 stage, and there were no side effects. Some patients reported improved sleep, increased exercises tolerance.

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SUMMARY

THE EFFECTIVENESS OF MELATONIN IN THE COMPLEX TREATMENT OF HYPERTENSION IN PATIENTS WITH STAGE 5 CHRONIC KIDNEY DISEASE

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In recent years, there has been a progressive increase in the number of patients with chronic kidney disease (CKD), whose mortality risk is significantly higher than in general patients, which is associated with cardiovascular risks.In patients with CKD stage 5D before the start of replacement renal therapy for hypertension exceeds 90%.

The aim -to analyze the efficacy and safety of the use of melatonin in the complex treatment of arterial hypertension (AH) in patients with CKD of 5 stage with impaired melatonin-forming function of the epiphysis (MFE).

60 people (35 women and 25 men) with a chronic kidney disease of 5 stage, which have violated MFE and AH were examined. For all patients in addition to antihypertensive therapy were prescribed the drug melatonin at a dose of 3 mg, which was taken once a day at 22:00 for 8 weeks. For all examined, before and after the course of treatment, were measured blood pressure (BP), Ambulatory Blood Pressure Monitoring (ABPM) and determination of the concentration of melatonin in the salivaby immunosorbent method.

The examined patients showed a high frequency of MFE disturbance both in the daytime and at night - respectively, in 52,4% ($p<0,001$) and 82,6% ($p<0,001$). The dynamics of the diurnal BP on the background of treatment was due to changes in the degree of nocturnal decrease of BP, the number of patients in the main group with the "non-dipper" profile, decreased from 44,5% to 27,6% ($p<0,05\%$), the proportion of patients with a daily profile of BP "night-peakear" from 22,4% to 4,8% ($p<0,05\%$). Besides, a statistically significant of the number of persons with a daily profile of BP "dipper" increase in 30,2%. Against the background of complex treatment, there was a decrease in the patient's need for the dose and amount of antihypertensive drugs to achieve BP targets.

Our data show a high incidence of MFE disorders in patients with CKD stage VD, and adding to the antihypertensive therapy of the drug melatonin in patients with CKD of 5 stage is effective and safe.

Keywords: arterial hypertension, chronic kidney disease, hemodialysis, melatonin,ambulatory blood pressure monitoring.

РЕЗЮМЕ

ЭФФЕКТИВНОСТЬ МЕЛАТОНИНА В КОМПЛЕКСНОМ ЛЕЧЕНИИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ У БОЛЬНЫХ ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК VД СТАДИИ

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Цель исследования - анализ эффективности и безопасности применения препарата мелатонин в комплексном лечении артериальной гипертензии пациентов с хронической болезнью почек VД стадии с нарушением мелатонинобразующей функции эпифиза.

Обследовано 60 больных, 35 женщин и 25 мужчин с диагнозом хроническая болезнь почек (ХБП) VД стадии с нарушением мелатонинобразующей функции эпифиза (МФЭ) и артериальной гипертензией. Всем больным дополнительно к антигипертензивной терапии назначался препарат мелатонин в дозе 3 мг, который принимали один раз в сутки в 22:00 в течение 8 недель. Всем обследуемым, до и после курса лечения, проводилось измерение артериального давления

(АД), выполнялся суточный мониторинг АД (СМАД) под контролем концентрации мелатонина в слюне иммуноферментным методом.

У обследованных пациентов отмечалась высокая частота нарушения МФЕ как в дневное, так и в ночное время – соответственно у 52,4% (p<0,001) и 82,6% (p<0,001). Динамика суточного профиля АД на фоне проводимого лечения развивалась за счет изменения степени ночного снижения АД, количество пациентов в основной группе с профилем «non-dipper», снизилась с 44,5% до 27,6% (p<0,05), доля пациентов с суточным профилем АД «night-peakear» с 22,4% до 4,8% (p<0,05). Отмечен статистически значимый прирост числа лиц с суточным профилем АД dipper на 30,2%. У пациентов основной группы дополнительно отмечалось уменьшение дозы и количества антигипертензивных препаратов.

Полученные в результате исследования данные указывают об эффективности и безопасности добавления к антигипертензивной терапии препарата мелатонин у пациентов с ХБП VД стадии.

რეზიუმე

მელატონინის ეფექტურობა არტერიული ჰიპერტენზიის კომპლექსურ მკურნალობაში პაციენტებში თირკმლების V-დ სტადიის ქრონიკული დაავადებით

ა.პეტროვა,ვ.კონდრატიუკი,ე.კარპენკო, ტ.ოსტაშევსკაია, ე. კრასიუკი

ა. ბოგომოლეცის სახ. ეროვნული სამედიცინო უნივერსიტეტი, კიევი, უკრაინა

კვლევის მიზანს წარმოადგენდა პრეპარატ მელატონინის გამოყენების ეფექტურობის და უსაფრთხოების ანალიზი არტერიული ჰიპერტენზიის კომპლექსურ მკურნალობაში პაციენტებში თირკმლების V-დ სტადიის ქრონიკული დაავადებით და ეპიფიზის მელატონინწარმომქმნელი ფუნქციის დარღვევით.

გამოკვლეულია 60 პაციენტი (35 ქალი, 25 მამაკაცი) თირკმლების V-დ სტადიის ქრონიკული დაავადების დიაგნოზით, რომელთაც გამოუვლინდათ ეპიფიზის მელატონინწარმომქმნელი ფუნქციის დარღვევა და არტერიული ჰიპერტენზია. ყველა ავადმყოფს, ანტიჰიპერტენზიულ თერაპიასთან ერთად, ენიშნებოდა პრეპარატი მელატონინი, დოზით 3 მგ, დღეში ერთხელ, 22 საათზე 8 კვირის განმავლობაში. ყველა გამოკვლეულს მკურნალობის კურსამდე და მის შემდეგ განესაზღვრა არტერიული წნევა,ნაუტარდა არტერიული წნევის დღელამური მონიტორინგი მელატონინის კონცენტრაციის კონტროლით ნერწყვში იმუნოფერმენტული მეთოდით.

გამოკვლეულ პაცინტებს აღენიშნა ეპიფიზის მელატონინწარმომქმნელი ფუნქციის დარღვევის მაღალი ხიხშირე როგორც დღის, ასევე, ღამის საათებში - შესაბამისად, 52,4% (p<0,001) და 82,6% (p<0,001). არტერიული წნევის დღელამური პროფილის დინამიკა ნატარებული მკურნალობის ფონზე გამოიხატა არტერიული წნევის დაქვეითებით ღამის საათებში. ძირითად ჯგუფში პაციენტების რაოდენობა პროფილით "non-dipper" შემცირდა 44,5%-დან 27,6%-მდე (p<0,05), პაციენტებისა დღელამური პროფილით "night-peakear" – 22,4%-დან 4,8%-მდე (p<0,05. ასევე, აღინიშნა სტატისტიკურად მნიშვნელოვანი, 30,2%-იანი ზრდა პირების არტერიული წნევის დღელამური პროფილით "dipper"; ძირითადი ჯგუფის პაციენტებში აღინიშნა ანტიჰიპერტენზიული პრეპარატების დოზისა და რაოდენობის შემცირება.

კვლევის შედეგები მიუთითებს ანტიჰიპერტენზიულ თერაპიაში მელატონინის ჩართვის ეფექტურობის და უსაფრთხოების შესახებ პაციენტებში თირკმლების V-დ სტადიის ქრონიკული დაავადებით და მელატონინწარმომქმნელი ფუნქციის დარღვევით.

ASSOCIATIONS BETWEEN EFFICACY OF THE THERAPY AND CIRCADIAN FLUCTUATIONS OF ENDOTHELIAL NITRIC OXIDE SYNTHASE WITH TOLL-LIKE RECEPTORS 2 EXPRESSION, AND NOS3 POLYMORPHISM IN FEMALES WITH RHEUMATOID ARTHRITIS

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Rheumatoid arthritis (RA) is an autoimmune polygenic disease characterized by a steadily progressing course and high resistance to treatment. Despite significant progress in understanding molecular mechanisms of RA and development on this basis new diagnostic and treatment approaches, the problem of resistance to the pharmacotherapy remains unsolved. About 40% of patients do not respond to basic disease-modifying antirheumatic drugs (DMARDs), 20% of which do not respond to combined therapy with use of biological agents [4,12,20].

The disturbance of circadian regulation of immune and inflammatory processes in articular tissues plays an important role in pathogenesis of RA [14]. New principles of synchronization of glucocorticoids, non-steroidal anti-inflammatory drugs and methotrexate with circadian rhythms of production hormones (melatonin, cortisol) and cytokines, are introduced to treatment in RA patients [7,23]. Therefore, the chronobiological aspects of resistance to the therapy in patients of different age and gender requires more detailed study. From this point of view, assessment of circadian rhythm in production of endothelial nitric oxide synthase (NOS3) and toll-like receptors 2 (TLR2) which involved in the regulation of angiogenesis [19,21], osteoclastogenesis [5,27] and in Th1/Th2 system balance modulation