DEPRESSIVE DISORDERS MANAGEMENT
IN ISCHEMIC HEART DISEASE PATIENTS

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OBJECTIVE: To study the dynamics of clinical, instrumental and psychological parameters in patients with ischemic heart disease (IHD) and comorbid depressive disorders on the stages of standard baseline therapy and additional tianeptine intake to develop proposals to improve management of such patients.

METHODS: 142 patients (77 males and 65 females) with the painful form of IHD in age from 45 to 60 years were examined. Quality of life (QoL), levels of depression, anxiety, pain perception; functional classes (FC) of stable angina pectoris and HRV indices were studied in patients with IHD in groups with a presence and absence of the depressive disorders at the beginning, in 3 weeks, 3, 6 and 12 months of baseline therapy and before and after 4 weeks of tianeptine adding to baseline therapy.

RESULTS: It was determined, that the depressive disorders result in worsening of QoL and HRV indexes. It was shown, that basic IHD therapy in the group of depressed patients with positive dynamics doesn't allow to achieve QoL and HRV indexes registered in the group of non-depressed patients. Also adding of tianeptine to baseline IHD therapy in depressed patients allows not only to improve QoL and HRV indexes, but also to attain the values of the proper indexes as in non-depressed group.

CONCLUSIONS: Patients with IHD should be examined for the presence of depressive disorders. In patients with IHD and clinically significant depression diagnosed antidepressant tianeptine must be added to baseline therapy.

KEY WORDS: ischemic heart disease, depressive disorders, heart rate variability, quality of life, tianeptine

ЛІКУВАННЯ ДЕПРЕСИВНИХ РОЗЛАДІВ У ПАЦІЄНТІВ
З ІШЕМІЧНОЮ ХВОРОБОЮ СЕРЦЯ

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МЕТА ДОСЛІДЖЕННЯ: вивчити динаміку клінічних, інструментальних і психологічних параметрів у пацієнтів з ішемічною хворобою серця (ІХС) та супутніми депресивними розладами на етапах стандартної терапії та її доповнення тіанептіном для розробки пропозицій щодо вдосконалення лікування таких хворих.

МЕТОДИ: У дослідження включили 142 пацієнтів (77 чоловіків і 65 жінок) з больовою формою ІХС у віці від 45 до 60 років. У всіх пацієнтів з ІХС в групах з наявністю і відсутністю депресивних розладів вивчали якість життя (ЯЖ), рівні депресії, тривоги, сприйняття больових відчуттів; функціональних класів (ФК) стабільної стенокардії і варіабельності серцевого ритму (ВСР) при початку, в 3 тижні, 3, 6 і 12 місяців стандартної терапії і до і після 4 тижнів додання до базисної терапії тіанептину.

РЕЗУЛЬТАТИ: Встановлено, що депресивні розлади призводять до погіршення якості життя і зниження показників ВСР. Було показано, що стандартна терапія ІХС у групі пацієнтів з депресивними розладами при позитивній динаміці не дозволяє досягти якості життя і значень ВСР, зареєстрованих у групі пацієнтів без депресії. Додання тіанептину до стандартної терапії у пацієнтів з депресивними розладами дозволяє не тільки поліпшити якість життя і ВСР, а й досягти значень, отриманих у групі пацієнтів без депресивними розладами.

ВИСНОВКИ: У пацієнтів з ІХС повинен проводитися скринінг на наявність депресивних розладів. У пацієнтів з ІХС та клінічно значущою депресією до стандартної терапії необхідно додання антидепресанту, наприклад тіанептину.

КЛЮЧОВІ СЛОВА: ішемічна хвороба серця, депресивні розлади, варіабельність серцевого ритму, якість життя, тіанептин

ЛЕЧЕНИЕ ДЕПРЕССИВНЫХ РАССТРОЙСТВ У ПАЦИЕНТОВ С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА

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ЦЕЛЬ ИССЛЕДОВАНИЯ: изучить динамику клинических, инструментальных и психологических параметров у пациентов с ишемической болезнью сердца (ИБС) и сопутствующими депрессивными расстройствами на этапах стандартной терапии и её дополнения тианептином для разработки предложений по совершенствованию лечения таких больных.

МЕТОДЫ: В исследование включили 142 пациентов (77 мужчин и 65 женщин) с болевой формой ИБС в возрасте от 45 до 60 лет. У всех пациентов с ИБС в группах с наличием и отсутствием депрессивных расстройств изучали качество жизни (КЖ), уровни депрессии, тревоги, восприятия болевых ощущений; функциональных классов (ФК) стабильной стенокардии и вариабельности сердечного ритма (ВСР) при начале, в 3 недели, 3, 6 и 12 месяцев стандартной терапии и до и после 4 недель добавления к базисной терапии тианептина.

РЕЗУЛЬТАТЫ: Установлено, что депрессивные расстройства приводят к ухудшению качества жизни и снижению показателей ВСР. Было показано, что стандартная терапия ИБС в группе пациентов с депрессивными расстройствами при положительной динамике не позволяет достичь качества жизни и значений ВСР, зарегистрированных в группе пациентов без депрессивных расстройств. Добавление тианептина к стандартной терапии у пациентов с депрессивными расстройствами позволяет не только улучшить качество жизни и ВСР, но и достичь значений, полученных в группе пациентов без депрессии.

ВЫВОДЫ: У пациентов с ИБС должен проводиться скрининг на наличие депрессивных расстройств. У пациентов с ИБС и диагностированной клинически значимой депрессией к стандартной терапии должен быть добавлен антидепрессант, например — тианептин.

КЛЮЧЕВЫЕ СЛОВА: ишемическая болезнь сердца, депрессивные расстройства, вариабельность сердечного ритма, качество жизни, тианептин

Ischemic heart disease (IHD) is one of the world's most prevalent disease of the cardiovascular system. IHD is the cause of more than half of all cardiovascular deaths [1]. It should also take into account the great socio-economic significance of IHD, which leads to a relatively early disability. Recent studies show that in addition to such factors as age, dyslipidemia [1], smoking, depressive disorders produce significant impact on the development, course and prognosis of the disease [2].

Depression in its various manifestations, including outpatient and inpatient patients with IHD occurs in 10–33 % of cases [3]. The frequency of depressive disorders in the population is 4,7–25,8 % in women and 2,1–12,3 % in men, and it is steadily progressing with age. Depressive disorders and heart disease are commonly comorbid [4]. The presence of depression is associated not only with a decreasing of patients' quality of life (QoL) [5], but also with an increased risk of cardiovascular complications [2] and death [6]. One possible pathogenetic mechanisms of the relationship of depression and cardiovascular disorders may appear imbalance between influences the para-sympathetic and sympathetic nervous systems [7].

Despite the current standards of therapy of IHD [1] the search for more effective medicines for the treatment of concomitant depressive disorders remains relevant. According to K. Beliles, in most cases antidepressants must be prescribed to control depression [8]. Due to the fact that tricyclic antidepressants have cardiotoxic effects [2], monoamine oxidase inhibitors and, rarely, serotonin reuptake inhibitors may lead to the development of severe hypotensive reactions, the choice of the safest antidepressant to treat depression in patients with IHD is quite problematic [9]. At the same time, long-term effectiveness of basic therapy and its impact on QoL indices and heart rate variability (HRV) in patients with IHD with concomitant depressive disorders were not covered in the literature. In particular, the possibility of baseline therapy complementing with tianeptine is not studied, although there are reasons to believe that this drug, which is well tolerated, have mild antidepressant and anxiolytic effects can be quite effective in such patients. A study of the mechanisms of physiological functions regulation in patients

with IHD and depressive disorders can provide significant aid in both predicting patient status and effective management of such patients.

Objective. To study the dynamics of clinical, instrumental and psychological parameters in patients with IHD and comorbid depressive disorders on the stages of standard baseline therapy and additional tianeptine intake to develop proposals to improve management of such patients.

MATERIALS AND METHODS

142 patients with painful form of IHD who were admitted to cardiology department «Central Clinical Hospital of Ukrainian Railways Ukrzaliznytsi». The duration of the study was from 2003 to 2006. Totally 77 males and 65 females aged 45 to 60 years (mean age for men — 49,7 ± 5,8, years, women — 54,0 ± ± 3,7 yrs.) were observed.

According to the criteria of the Canadian Cardiovascular Society all patients had stable angina pectoris ranged from I to III functional classes (FC). I FC of stable angina pectoris (SAP) was found in 45 patients (32 ± 4 %), II FC — in 52 (36 ± 3 %) and III FC — in 45 patients (32 ± 4 %). 57 patients had previous acute myocardial infarction (AMI) with subsequent development of post-infarction cardiosclerosis (PICS). In 132 patients chronic heart failure (CHF) of FC I–III according to New York Heart Association (NYHA) classification and I–IIA stages according to Ukrainian Scientific Society of Cardiology classification was diagnosed. I FC of CHF according to NYHA classification was detected in 27 (19 ± 3 %), II FC CHF — in 76 (53 ± 3 %) and III FC CHF — in 32 patients (21 ± 3 %); I stage heart failure according to Ukrainian Scientific Society of Cardiology classification was detected in 85 patients (60 ± 3 %), II A stage — in 29 (20 ± 5 %). 123 patients had concomitant arterial hypertension (AH). According to the criteria of the Ukrainian Association of Cardiology [10], a mild degree was found in 33 of them (23 ± 3 %), moderate — in 61 (35 ± 3 %) and severe — in 28 (19 ± 3 %).

64 patients had depressive disorders according to the criteria of the International Classification of Diseases, 10th revision (WHO, 1995). Thus somatogenic depression (F06.32) was noted in 9 patients, psychogenic depression (F43.21) was met in 33 patients (52 ± 6 %), endogenous depression (F32.0–F32.2) was met in 22 patients (34 ± 5 %).

The inclusion criteria was a painful form of IHD with stable angina pectoris I–III FC.

Exclusion criteria were: stable angina pectoris IV FC, acute myocardial infarction, valvular defects, heart failure IIb–III stages, IV FC CHF, implanted pacemakers, AV conduction disorders, endocrine disorders (diabetes, thyroid disease), peptic and duodenal ulcer in acute phase, renal and hepatic failure, acute cerebrovascular events or its consequences.

Research methods. In all patients were assessed Ferrans & Powers quality of life (QoL) overall and in four domains: health/functioning, psychological/spiritual, social/economic, and family [11], the levels of depression and anxiety with HDRS and HADS scales, pain perception with McGill Pain Questionnaire (MPQ), blood pressure on both arms, heart ultrasound. Heart rate variability (HRV) assessment was conducted in accordance with the recommendations of the Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [12] — total power (TP) of HRV spectrum and its components — domains of very low frequency (VLF, associated of neurohumoral regulation and heat regulation), low (LF, relating to the regulation of sympathetic link), high (HF, associated with the element of parasympathetic regulation). Also the ratio LF/HF was determined which is considered as a measure sympathovagal balance.

At first 103 patients with IHD were examined — 60 males and 43 females. The study showed that in 25 observed patients (24 %, 11 males and 14 females), depressive disorders were found. Second, 39 IHD patients (17 males and 22 females) with concomitant depressive disorders were additionally included in a study for a more detailed study of depressive disorders in patients with IHD.

Patients were divided into 2 groups: the first group (64 patients) had depressive disorders while the second group (78 patients) did not. The distribution of patients into groups was based on the presence or absence of criteria for depressive disorders according to ICD-10 and on the results of HDRS.

Therapy was performed in two phases: In first phase all patients in both groups received baseline therapy, as recommended by the Ukrainian Association of Cardiology [1], in the second phase in patients with depressive disorders tianeptine was added to basic therapy. The duration of the first phase was 1 year, the

second — 4 weeks. Registration of QoL and HRV indices was performed in the first stage before treatment, after 3 weeks, 3 months. 6 months. baseline and 1 year of therapy and the second stage — after 4 weeks of tianeptine intake.

Baseline therapy included beta-blockers, calcium channel blockers, aspirin, statins and nitrates [1]. Tianeptyn administered 12,5 mg 3 times a day.

The criteria for the efficacy of therapy were: QoL and HRV improvement, SAP FC decline.

Statistical procedures included mean (M), standard deviation (sd), parametric and non-parametric tests: Student's t-test, T-Wilcoxon test (for related samples) and Mann-Whitney U-test (for independent samples) [13]. For the determining the probability of differences between groups 95 % confidence interval (CI) was used. Frequency characteristics of indices studied — the percentage (%) and the percent deviation (pD) was calculated [14].

RESULTS AND DISCUSSION

In the group of depressed patients prevailing of women were observed, with higher angina and CHF FCs, degree of hypertension, higher scores of MPQ. In contrast, in the group of non-depressed patients dominance of males were observed, lower angina and CHF FCs and lower incidence of hypertension (Table 1).

Table 1

Clinical characteristics of patients with painful form of IHD in groups with the presence and absence of depressive disorders, (M ± sd; n (% ± pD))

Index			Groups	
			Depressed patients (64)	Non-depressed patients (78)
Sex	Male		28 (44 ± 6)	49 (63 ± 5)
	Female		36 (56 ± 6)	29 (37 ± 5)
Age, years (M ± sd)			51,16 ± 6,17	51,61 ± 5,31
IHD	SAP FC	I	10 (16 ± 4)	35 (45 ± 5)
		II	21 (33 ± 6)	31 (40 ± 5)
		III	33 (51 ± 5)	12 (15 ± 4)
	AP FC (M ± sd)		2,36 ± 0,74	1,71 ± 0,72
Quantity of patients with PICS			29 (45 ± 6)	28 (36 ± 5)
CHF	FC	I	10 (16 ± 4)	17 (22 ± 4)
		II	31 (48 ± 6)	45 (58 ± 5)
		III	18 (28 ± 5)	11 (14 ± 3)
	(M ± sd)		1,96 ± 0,87	1,79 ± 0,76
	Stage	I	41 (64 ± 6)	44 (56 ± 5)
		IIA	20 (31 ± 6)	12 (15 ± 3)
Quantity of patients with AH			61 (95 ± 2)	62 (79 ± 4)
AH stage	1		6 (9 ± 3)	27 (35 ± 5)
	2		40 (63 ± 6)	21 (27 ± 5)
	3		15 (23 ± 5)	13 (17 ± 3)
MPQ, points			17,21 ± 3,1	14,37 ± 3,74

Initially, in group of depressed patients were observed significantly lower levels (p < 0,05) of QoLI (12,4 ± 1,04 points vs 16,7 ± 1,8), health and functioning (9,8 ± 1,0 points vs. 13 5 ± 1,3), psychological/ spiritual (10,3 ± 1,2 points vs 15,0 ± 1,9) and family (15,3 ± 1,9 points vs 20,3 ± 2,6) and insignificantly lower social and economic domains (14,9 ± 1,9 points vs 18,3 ± 3,4) (p > 0,05) comparing with the group of non-depressed patients.

Also obtained results indicate that initially in group of depressed patients in comparison with group of non-depressed patients were observed significantly higher depression levels measured by HDRS (12,1 ± 1,8 points vs 5,6 ± 2,0) and HADS (12 ± 1,6 points vs 4,4 ± 1,9) scales and the anxiety levels measured by HADS scale (8,0 ± 1,3 points vs 4,2 ± 2,3) (p < 0,05).

HRV research showed a similar pattern — in group of depressed patients were observed lower TP (497,24 ± 298,37 ms^2 vs 769 ± 386), VLF (253 ± 147 ms^2 vs 392 ± 217), LF (167 ± 115 ms^2 vs 249 ± 198), HF (77 ± 76 ms^2 vs 132 ± 141) and the ratio LF/HF (2,78 ± 1,32 vs. 3,5 ± 3,49) indices comparing with group of non-depressed patients

(p > 0,05). This pattern, which was observed in both groups, indicates that depression leads to changes in autonomic balance toward activation of sympathoadrenal system, reducing the efficiency baroreflex regulation and stress regulatory systems, which has an adverse prognostic significance.

Results obtained on further stages of the study showed that the most pronounced improvement in QoL, decline in depression and anxiety levels, pain perception (MPQ), SAP FC was achieved in the early stages of the study (3 weeks and 3 months of basic therapy) where further minor variations of these indicators were registered.

Despite the positive trend in patients with depressive disorders in comparison with the group of patients without depressive disorders QoL, decline in depression and anxiety levels, pain perception (MPQ), SAP FC still remained significantly higher.

Also, despite the presence of significant positive improvement of HRV indices, even after 1 year of baseline treatment in patients with depressive disorders compared with a group of patients with depressive disorders ratio LF/HF still remained higher (p > 0,05), and

TP, VLF, LF and HF indexes — lower (p < 0,05). Thus, despite the positive dynamics in patients with depressive disorders (increased total power and its subdomains, including parasympathetic level, sympathovagal balance normalization) as previously observed decrease in the power spectrum of HRV, occurs excessive sympathetic activation and parasympathetic inhibition. Based on the concept that the cardiovascular system is an indicator of the body's adaptive abilities such HRV indices that depression leads to a decrease in the functional capacity of the organism and increase the «price» for physiological adaptation in patients with depressive disorders.

The aim of the next study stage was to explore the influence of tianeptine intake on QoL, depression and anxiety levels in patients with IHD with depressive disorders.

Tianeptine intake in a standard dose of 37,5 mg for 4 weeks in a group of patients with depressive disorders allowed to increase QoL levels, decrease depression and anxiety levels, lower pain perception (MPQ) results and increase all HRV indices (TP, VLF, LF and HF) (Table 2).

Table 2

Quality of life, depression and anxiety levels and HRV indices on different sudy phases in group of depressed patients (M ± sd)

Indices	Study stages				
	1st phase — baseline therapy			2nd phase — adding of tianeptine to baseline therapy	
	Admittance	3 weeks	1 year	Initially	4 weeks
QoL, (M ± sd)	13,7 ± 3,14	14,8 ± 2,94	15,5 ± 3,54	15,9 ± 3,14	22,1 ± 3,6123
HDRS, (M ± sd)	12,3 ± 3,94	11,2 ± 3,74	11,1 ± 3,44	11,0 ± 3,24	3,2 ± 1,5123
HADS, depression scale, (M ± sd)	8,4 ± 3,44	8,1 ± 2,84	7,5 ± 2,34	7,3 ± 2,74	3,4 ± 1,2123
HADS, anxiety scale (M ± sd)	5,1 ± 2,13,4	4,6 ± 1,7	2,8 ± 1,41	2,7 ± 1,61	2,1 ± 0,712
TP BCP, мс^2	759 ± 1664	767 ± 189	981 ± 219	1066 ± 2311	1278 ± 2531,2
VLF, мс^2	442 ± 1044	474 ± 126	597 ± 114	633 ± 1491	654 ± 113,71,2
LF, мс^2	249 ± 564	287 ± 52	306 ± 68	335 ± 75	456 ± 103 1,2
HF, мс^2	65 ± 23,44	76 ± 35,1	84 ± 29,7	98 ± 34	159 ± 68,712
LF/HF	4,1 ± 1,3	3,9 ± 1,1	3,8 ± 1,0	3,7 ± 1,1	2,9 ± 1,2

Notes:
[1] — the differences comparing to the levels on admittance point are significant;
[2] — the differences comparing to the results on 3rd week of the first phase of treatment are significant;
[3] — the differences comparing to the results after 12 months are significant;
[4] — the differences comparing to the results for the 4th week of tianeptine intake are significant

Our data about greater burden of IHD course due to the depressive disorders is supported by recent publications, e. g. article by O. Mittag and T. Meyer, confirming that association of depression and IHD seems independent from pivotal demographic variables (gender, marital status or education) [15].

Similar results were obtained by GV Pogosov and et al. [16], where the authors noted significant QoL improvement in patients with IHD on the background of baseline IHD ther-

apy and tianeptine intake in dose 37,5 mg daily for 6 weeks.

Increase of HRV indices (TP, VLF, LF and HF) and decreasing of LF/HF ratio in patients receiving tianeptine was not reflected in the literature, but similar results were obtained in a study by AV Trofimov et al. [17]. Dynamics of the HRV indices in patients with acute MI and depressive disorders while taking paroxetine were studied. As a result of paroxetine intake in patients with MI were reduction of depressive symptoms and a more favorable course of postinfarction period. In addition, were found significant increasing HRV indices, accompanied by a significant increase in parasympathetic influences.

Significant decline in the subjective perception of pain on a MPQ scale when adding tianeptine to baseline treatment of IHD in patients with depression was not reflected in the literature also.

CONCLUSIONS

1. Among the IHD patients with depressive disorders compared with the group without depressive disorders higher SAP FC (p > 0,05), CHF FC (p > 0,05) and the degree of hypertension, higher values of depression and anxiety (p < 0,05), higher values on a scale perception of pain MPQ (p > 0,05), lower rates of capacity HRV (TP, VLF, LF and HF) (p > 0,05) were observed.

2. In the group of patients with depressive disorders comparing with patients without depression lower QoL levels, health and functioning, psychological/spiritual, family, social and economic QoL domains were also observed.

3. Despite positive changes when using baseline therapy in patients with IHD and depressive disorders compared with patients without depression higher levels of depression and anxiety (p < 0,05), pain perception MPQ (p > 0,05), SAP FC (p > 0,05) and lower — QoL levels, health and functioning, psychological/spiritual (p < 0,05), social and economic (0,1 > p > 0,05), family domains (p > 0,05).

4. In IHD patients with in the presence and the absence of depressive disorders baseline therapy enables achieve improvements in all indices of HRV spectrum and reduce the LF/HF ratio (p > 0,05), but at the same time in patients with depressive disorders lower (p > 0,05) spectral indices and higher LF/HF ratio of (p < 0,05) are found, compared with patients without depressive disorders, indicating the exhaustion of adaptation reserves and an imbalance of autonomic regulation in patients with depressive disorders.

5. Adding tianeptine to baseline therapy in all patients with IHD and depressive disorders helps to achieve increasing of QoL to levels observed in patients without depressive disorders and optimizing HRV indices and reduce the LF/HF ratio almost to the level observed in the absence of depressive disorders.

6. Patients with IHD should be examined for the presence of depressive disorders. In patients with IHD and clinically significant depression diagnosed antidepressant tianeptine must be added to baseline therapy.

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