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ORIGINAL ARTICLE

Cardiology

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Factor Analysis of Predicting Cardiovascular Death in the Remote Period after Myocardial Revascularization

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Abstract

The aim of the present study was to analyze the impact of traditional and renal risk factors (RFs) on the probability of cardiovascular death in CHD patients in the remote period after myocardial revascularization (MR).

Materials and Methods: The present study included 90 CHD patients (80 men and 10 women; mean age 56.1±0.9 years) with indications for MR. The prevalence of major cardiovascular RFs (old age, gender, duration of CHD, arterial hypertension, diabetes mellitus, another localization of atherosclerotic lesions, and the presence and duration of smoking) and the main echocardiographic parameters and the parameters of renal function (MAU and GFR) were assessed. Fatal cardiovascular outcomes were the only endpoint of the study.

Results: Cardiovascular death (CVD) occurred in 10/12.3% patients. The studied RFs, such as the patient's age, duration of smoking, and presence of angina with low tolerance to physical stress, had a significant impact on the probability of death in CHD patients. Risk of CVD (rCVD) over a long-term period increases by 18.1% in patients with elevated levels of total cholesterol, by 16.2% in patients with stable angina pectoris class III, by 50.5% in patients with atherosclerotic lesions of lower limb and cerebral arteries, and by 69.3% in patients suffering from overweight. Left atrial size, LVPWT, and LVMI were also significant predictors of adverse cardiovascular prognosis. The increase in the number of coronary arteries with clinically significant stenosis, including subtotal narrowing of the vessel lumen, increases rCVD in the long-term period. The important role of a highly reliable level of glucose in the urine for the risk score was found. The presence of CKD stage 3 and the impaired GFR also significantly increased rCVD.

Conclusion: Our data demonstrate a high medical and social importance of a comprehensive and integrated analysis not only of traditional RFs, but also of markers of renal dysfunction in risk stratification of cardiovascular prognosis in CHD patients. **(Int J Biomed. 2015;5(3):117-122.)**

Keywords: *coronary heart disease (CHD); myocardial revascularization; risk factors; prognosis.*

Abbreviations: LVEDD, left ventricular end-diastolic dimension; **LVESD**, left ventricular end-systolic dimension; **LVEDV**, left ventricular end-diastolic volume; **LVESV**, left ventricular end-systolic volume; **IVST**, interventricular septal thickness; **LVPWT**, left ventricular posterior wall thickness; **LVMI**, left ventricular mass index; **LVEF**, left ventricular ejection fraction; **GFR**, glomerular filtration rate; **MAU**, microalbuminuria.

Introduction

Prediction of the risk of cardiovascular complications is a priority for preventive medicine, cardiology, and intensive care [1,2]. This is due to the severe consequences of diseases of the cardiovascular system that occur in connection with structural adjustment and persistent dysfunction of the heart and other organs and systems. These consequences are caused by many pathological mechanisms, including hyperactivity of neurohumoral systems. Cardiac and renal disorders are closely correlated with formation of a vicious circle that leads to progressive worsening of a patient's prognosis. Cardio-renal continuum plays an important role in the prediction of cardiovascular and renal survival [3,4]. In many clinical

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studies, decreasing of renal function was found in patients with arterial hypertension [5] and chronic heart failure [6]; however, the existence of mutually reinforcing pathogenetic relations has been less studied in coronary heart disease (CHD).

Patients with coronary artery disease undergoing coronary reperfusion are a cohort with the highest cardiovascular risk. Operations to restore coronary blood flow are a paramount method of treatment, improving the quality of life in CHD patients. Reducing risk of death and cardiovascular complications is also the purpose of myocardial revascularization (MR). This target is feasible only for a short period of time because mechanical correction of myocardial ischemia is not a means of regulating the pathogenetic mechanisms of CHD progression. The occurrence of restenosis of the coronary arteries and deterioration of cardiovascular prognosis depends on two main factors – the compliance of the patient with optimal medical therapy and the factor environment of the patient. Study of the effect of risk factors (RFs), including markers of renal dysfunction, on the long-term cardiovascular prognosis of patients undergoing surgical MR is a priority for secondary prevention in this cohort of patients. Risk stratification of cardiovascular complications, including cardiovascular death (CVD), is designed to assess the contribution of RFs according to their importance in the formation of the prognosis and to determine the tactics of their correction.

The aim of the present study was to analyze the impact of traditional and renal RFs on the probability of CVD in CHD patients in the remote period after MR.

Materials and Methods

The present study included 90 CHD patients (80 men and 10 women; mean age 56.1±0.9 years) with indications for restoration of coronary blood flow. Coronary angiography was performed in all patients to determine the presence and the degree of luminal obstruction of the coronary arteries and to assess the feasibility and appropriateness of various forms of therapy, such as revascularization by percutaneous or surgical interventions. Data of coronary angiography are presented in Table 1.

Table 1.

Coronary angiographic parameters in CHD with indications MR

Variable	Value
Coronary atherosclerosis, number of arteries	2.06±0.09
Subtotal CAS, number of arteries	2.03±0.1
Hemodynamically insignificant CAS, number of arteries	0.1±0.03
Occluded coronary arteries, number of arteries	0.4±0.06
Clinically significant CAS, number of arteries	2.7±0.2
Maximal coronary artery stenosis, %	89.1±1.04

CAS- Coronary artery stenosis

Coronary artery bypass grafting (CABG) was conducted in 64/57.6% patients and percutaneous coronary intervention (PCI) with stent implantation in 26/42.4% patients. At the beginning of the study, we assessed the prevalence of major cardiovascular RFs: old age, gender, duration of CHD, arterial hypertension (AH), diabetes mellitus (DM), another localization of atherosclerotic lesions, and the presence and duration of smoking. We then estimated the main echocardiographic parameters (LVEDD, LVESD, LVEDV, LVESV, IVST, LVPWT, LVMI, and LVEF**)** and the parameters of renal function – MAU and GFR. MAU (urinary albumin excretion of 30-300 mg/24 hours) was assessed by a semi-quantitative method using test strips for the determination of protein in the urine, in compliance with the rules for collecting morning urine. GFR was estimated by the Cockcroft-Gault formula. Stages of chronic kidney disease (CKD) were determined according to the KDOQI 2002 classification. Patients with CKD stages 4-5 were excluded from this study.

Table 2 presents the data on the prevalence of the studied RFs and the severity of the clinical parameters of the patients.

Table 2.

Traditional cardiovascular RFs and clinical status of CHD patients

Variable	Value
Age, years	56.1±0.9
Patients with excess body weight, abs (%)	34 (37.8)
Smoking patients, abs (%)	32 (35.6)
Total cholesterol, mmol/l	5.65±0.15
High-density lipoprotein, mmol/l	1.1±0.03
Low-density lipoproteins, mmol/l	4.6±0.2
Triglycerides, mmol/l	1.95±0.1
Dyslipidemia, type IIa, abs (%)	47 (52.2)
Dyslipidemia, type IIb, abs (%)	29 (32.2)
LVEDV, ml	151.2±3.9
LVESV, ml	72.3±3.01
LVEF, %	53.0±0.7
IVST, mm	12.53±0.17
LVPWT, mm	11.99±0.15
Angina pectoris class II, abs (%)	5 (5.6)
Angina pectoris class III, abs (%)	73 (81.1)
Angina pectoris class IV, abs (%)	1 (1.1)
Unstable angina, abs (%)	8 (8.9)
Acute myocardial infarction, abs (%)	3 (3.3)
Myocardial infarction, abs (%)	66 (73.3)
Arterial hypertension, abs (%)	77 (85,6)
Diabetes, abs (%)	19 (21.1)
Atherosclerosis of the lower limb arteries, abs (%)	7 (7.8)
Atherosclerosis of the cerebral arteries, abs (%)	4 (4.4)
MAU, mg/24 hours	0.15±0.02
The presence of MAU, abs (%)	82 (91.1)
GFR, ml/min	90.2±2.2
The presence of CKD, abs (%)	88 (97.8)
CKD stage 1, abs (%)	48 (54.5)
CKD stage 2, abs (%)	33 (37.5)
CKD stage 3, abs (%)	7 (8.0)

The study was conducted in accordance with ethical principles of the Declaration of Helsinki and approved by the Rostov State Medical University Ethics Committee. Written informed consent was obtained from all participants.

The study included 4 stages. Stage 1: determining the presence and severity of traditional/renal RFs, as well as the severity of the clinical condition of patients. Stages 2, 3, and 4: monitoring of existing RFs and evaluation of the clinical status of the patients on 5.9±0.2 days, 6.3±0.1 months, and 5.8±0.05 years after MR, respectively. In the remote period after MR, the number of patients participating in the fourth phase of the study amounted to 71/78.9%. Fatal cardiovascular outcomes were the only endpoint of the study. CVD occurred in 10/12.3% patients.

Statistical analysis of data was performed using the software Statistica 8.0. The mean (M) and standard deviation (SD) were calculated. Differences of continuous variables with a normal distribution between the two groups were calculated using the independent-sample *t*-test. Group comparisons with respect to categorical variables are performed using chi-square tests. Two-tailed *P* values <0.05 were considered statistically significant.

Results

We determined that the studied RFs, such as the patient's age, duration of smoking, and presence of angina with low tolerance to physical stress, had a significant impact on the probability of death in CHD patients. According to logistic regression analysis (LRA), the risk of cardiovascular death (rCVD) in the remote period after MR in patients of the 35-year-old age group at the time of the MR is minimal and amounts to 0.9%; rCVD is 2.4% to 6.3% in the 45-to-55 year age group and increases significantly up to 15.4% to 33.2% in the 65-to-75 year age group (*P=0.02*). Addiction to smoking is one of the most common and significant factors of cardiovascular risk. We have found that smoking has a significant impact on rCVD in the remote period after MR. A ten-year smoking history leads to an increase in rCVD up to 5.7%; a 20-year history, up to 8.3%; a 30-year history, up to 11.9%; and a 50-year history, up to 23.1% (*P=0.04*). LRA demonstrated that rCVD over a long-term period increases by 18.1% in patients with elevated levels of total cholesterol determined before revascularization compared with patients who achieved target values of lipid parameters (*P=0.03*). After 5.8±0.05 years following MR, rCVD is increased by 16.2% in patients with stable angina pectoris class III (CCS) compared with patients with better exercise tolerance (*P=0.04*). Atherosclerotic lesions of lower limb and cerebral arteries increases rCVD in the remote period after MR by 50.5% (*P=0.02*), whereas patients suffering from overweight have rCVD amounting to 69.3% (*P=0.02)*. Type 2 DM showed no significant deterioration of the cardiovascular prognosis in the long term after MR when taking into account only the fact of DM presence (*P=0.02*). However, LRA allowed us to demonstrate the important role of a highly reliable level of glucose in the urine for the risk score. When glucosuria is 0.2 g/l, rCVD is 17.6%, whereas it increases by 43% (*P=0.005*) with increasing glycosuria up to 0.8 g/l. The relationship between glycosuria levels and rCVS of CHD patients in the remote period after MR is presented in Figure 1.

Left atrial size (*P=0.02*), LVPWT (*P=0.02*), and LVMI (*P=0.02*) were also significant predictors of adverse cardiovascular prognosis. Risk of CVD in the remote period after MR according to echocardiographic parameters is presented in Table 3.

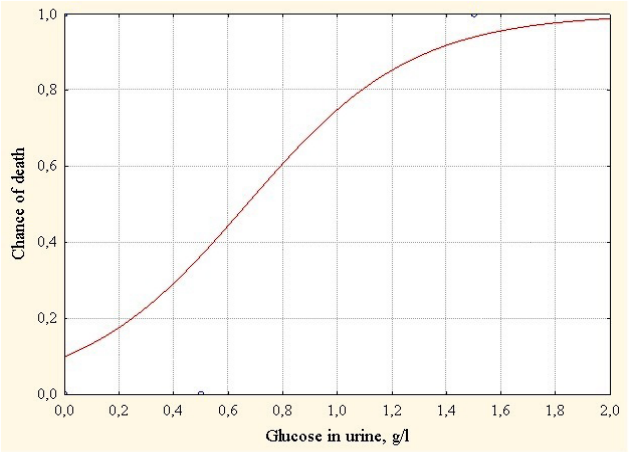

Fig 1. *The probability of CVD in CHD patients in the remote period after MR according to the level of glucose in the urine*

Table 3.

rCVD in the remote period after MR according to echocardiographic parameters

	Left atrial size, mm				
	20	30	40	50	60
Chance of death, %	0.4	2.4	10.8	37.5	74.8
	LVPWT, mm				
	9	11	13	15	17
Chance of death, %	1.8	5.3	14.3	33.4	60.1
	LVMI, g/cm^3				
	140	180	220	260	300	340
Chance of death, %	8.0	16.2	30.2	49.0	68.1	82.6

Analysis of renal RFs allowed us to establish a high prevalence of renal dysfunction in CHD patients with indications for MR. The prevalence of MAU amounted to 91.1% of cases with an average level of 110±7mg/day; the incidence of CKD amounted to 97.8% of cases. We have not found a significant impact of MAU on rCVD. However, LRA revealed a highly significant influence of other indicators of renal dysfunction on rCVD. The presence of CKD stage 3 increases rCVD in the period before MR (58.8%; *P<0.001*) and in the late period (6.3±0.1 months) after MR (27.9%; *P=0.02*). The impaired GFR, defined later, 5.9±0.2 days after MR significantly increases rCVD (*P=0.04*) (Fig.2).

We studied also the characteristics of coronary lesions. The increase in the number of coronary arteries with clinically significant stenosis (*P=0.03*), including subtotal narrowing of the vessel lumen (*P=0.03*), increases rCVD in the long-term period. Stratification of rCVD in the remote period after MR is presented in Table 4. Obviously, the increased rCVD in CHD

patients occurs when the severity of myocardial ischemia is exacerbated due to the number of atherosclerotic-affected coronary arteries and the degree of stenosis.

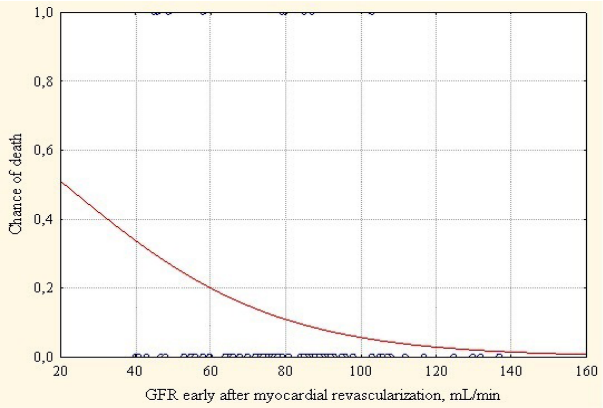

Fig.2. *The probability of CVD in CHD patients in the remote period after MR according to the value of GFR*

Table 4.

The probability of CVD in CHD patients in the remote period after MR according to the severity of coronary lesions

	Clinically significant CAS, number of arteries					
	1	2	3	4	5	6
Chance of death, %	5.3	7.8	11.4	16.4	22.9	31.1
	Coronary artery subtotal stenosis, number					
	1	2	3	4	5	6
Chance of death, %	6.3	10.3	16.4	25.2	36.6	49.8

Discussion

The importance of predicting the risk of cardiovascular complications is determined by the high prevalence of cardiovascular diseases, mortality, and the reduced quality of life of patients suffering from cardiovascular diseases [7]. According to the latest WHO report (Inf. Bulletin No. 317, Jan 2015), 17.5 million people died from cardiovascular diseases in 2012, which corresponds to 31% of all causes of death in the world. It is important that 14.1 million deaths were caused by CHD and acute cerebral accidents with the primary contribution of myocardial ischemia to the mortality structure. Patients included in our study had a high cardiovascular risk because of a large prevalence of traditional and renal RFs. Every third patient had a history of being overweight addicted to smoking, and almost all patients did not achieve target levels of cholesterol. We registered cardiovascular accidents in patient histories and the presence of hypertension in the most cases. The severity of the clinical condition and a large number of RFs explain the high mortality rate in the remote period after MR.

The age of CHD patients is a well-known RF of the disease progression. According to H. Ao [8], the risk of death after having coronary reperfusion performed significantly increased in the older cohort of patients compared with younger patients. Our study also demonstrated the great importance of assessing the patient's age. Smoking is the most well-known predictor of cardiovascular complications [9]. The results of many studies indicate that a poor prognosis for cardiovascular diseases depends not only on smoking, but also on the duration of nicotine dependence. According to a study by L.S. Rallidis [10] conducted on a cohort of young patients aged less than 35 years who have had an acute MI, it has been shown that there is a significant increase in risk of cardiovascular events (death, acute coronary syndrome, revascularization) with increased duration of smoking. At the same time, some studies have demonstrated conflicting evidence. A study conducted on a group of 8,671 CHD patients with MR shows that there were no significant differences in the incidences of angiographic restenosis between groups of patients who smoked and those who had no nicotine dependence, whereas the clinical manifestations of myocardial ischemia were more often registered in non-smoking patients [11]. The authors of the study attribute the differences to the decreased sensitivity to myocardial ischemia in smoking patients and a reluctance to consult a doctor in cases of recurrent angina. The results of other studies indicate an increasing probability of death and acute MI after coronary reperfusion in patients with a long history of smoking [9,12]; quitting smoking before or after revascularization significantly reduced the risk of adverse cardiovascular complications in study by T.Chen [9]. The analysis of present study confirms the adverse effect of smoking duration on cardiovascular prognosis and demonstrates its impact on mortality in the remote period after MR.

The relationship between the severity and prevalence of myocardial ischemia and an increased risk of cardiovascular complications is not in doubt [13]. We have shown that rCVD in the remote period after MR increases with an increase in the number of the atherosclerotic affected arteries with clinically significant stenosis, including subtotal stenosis. The presented data on the increase in the probability of death in the remote period in patients with peripheral atherosclerosis and ischemic disease of the brain fit into the concept of atherosclerosis as a generalized process.

Mechanisms that regulate glucose homeostasis in the kidneys are controlled primarily by transport proteins engaged in the reabsorption of glucose in the proximal renal tubules. It is known that there is a complete return absorption of glucose up to its absence in the secondary urine under physiological conditions. The system of protein transport carries out the glucose reabsorption even under conditions of hyperglycemia. Depletion of protein transporters with the subsequent glycosuria occurs when the threshold concentration of blood glucose is greater than 10 mmol/l (180 mg/dl) [14]. Many studies on the pathological influence of uncontrolled hyperglycemia exhibit an increased risk of developing macro- and microvascular complications [14]. We found that the likelihood of increased risk of death in the remote period after MR depends on an increase in the urine glucose level, while there were no data indicating increased rCVD in DM patients.

Echocardiographically determined left atrial size has been shown to be a significant predictor of cardiovascular

complications in patients with various cardiovascular diseases [15]. The increased left atrial size is a marker of adverse cardiovascular prognosis in patients with atrial fibrillation [16], acute MI [17], in elderly patients with or without cardiac arrhythmias [18], and heart failure [16]. Many studies, including ours, have identified an association between the increased left atrial size and an increase in the probability of death in patients suffering from myocardial ischemia. The results can be explained by the known data indicating that the increased left atrium is closely associated with overproduction of atrial natriuretic peptide (ANUP) that is an independent predictor of cardiovascular complications. We also found that myocardial ischemia is one of the factors causing the increase in ANUP formation as a result of myocardial remodeling that occurs in response to ischemia [19].

Myocardial hypertrophy is one of the important echocardiography markers in the cardiovascular risk stratification. The increased LVMI and left ventricular wall thickness, emerging due to high blood pressure, increases the risk of cardiovascular death, as shown in the famous Framingham Heart Study [20]. In our study, we have also shown that left ventricular hypertrophy affects the risk of death for patients in the remote period after MR.

Currently, an identification of renal RFs is one of the priority positions in the research finding. It is a proven fact that renal dysfunction has an impact on the risk of cardiovascular complications in patients with socially significant cardiac pathology. Our earlier research has demonstrated the high importance of the magnitude of MAU. The risk of coronary events has been increased by 5% with a 2-fold increase in the minimum MAU level in patients before coronary intervention; the risk increased further by 7% at maximum MAU level [21]. The risk of recurrent angina in patients with CKD stage 3 was significantly higher in the late period (6.3±0.1 months) after MR [22]. We have found the great contribution of reduced GFR on rCVD in patients undergoing surgical MR. The reliability of the obtained data was established for CKD stage 3, which was shown for the initial period before coronary reperfusion and in the late period of surgical intervention. The obtained data confirm the importance of determining markers of renal dysfunction as reliable predictors of CHD progression and the selection of the group of patients with a high probability of dying in the remote period after revascularization. There is a dependence of rCVD on GFR values, which is determined in a short period after MR. The frequency of having to perform acute dialysis after surgical interventions on the heart is from 1% to 5% of cases [23[. Mechanisms of kidney injury in cardiac surgery are multifactorial and include a number of key conditions – low cardiac output, hypoperfusion and ischemia of the kidney tissue, and loss of pulsating flow of blood circulation [24]. M.L. Felicio et al. [24] showed that a significant decrease in GFR occurs in patients after coronary artery bypass surgery. We have also demonstrated that a significant decrease in GFR is observed in the early period after MR and after 6.3±0.1 months after coronary reperfusion compared with the period before MR. The decrease of GFR in the short and long period after MR can be interpreted as a decrease in the functionality of the renal tissue in conditions of hemodynamic imbalance. The degree of GFR reduction indicates the severity of impairments in the heart-kidney relationships and determines the prognosis of cardiovascular complications.

Conclusion

Data obtained from our study demonstrate a high medical and social importance of a comprehensive and integrated analysis not only of traditional RFs, but also of markers of renal dysfunction in risk stratification of cardiovascular prognosis in CHD patients. A comprehensive analysis of RFs should be performed on every CHD patient with indications for restoration of coronary blood flow. This will help optimize the clinical condition of the patient and timely correction of existing RFs.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

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Effect of Radiofrequency Catheter Ablation on Quality of Life in Patients with Wolff-Parkinson-White Syndrome

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Abstract

Wolff-Parkinson-White (WPW) syndrome is one of several disorders of the conduction system of the heart that are commonly referred to as pre-excitation syndromes. As the syndrome significantly reduces the patients' quality of life (QoL), the purpose of the current study was to compare QoL scores in patients with WPW syndrome before and after a radiofrequency catheter ablation (RFA) procedure. To assess the patients' QoL, the MOS 36-Item Short-Form Health Survey was used. Immediate and long-term outcomes of radiofrequency catheter ablation were analyzed in 60 patients diagnosed with WPW syndrome, 41(68.3%) men and 19(31.7%) women. As compared with the controls (28 apparently healthy persons), patients with WPW syndrome before RFA experienced significant reduction in both physical and mental health components. RFA was found effective in 93.3% of patients with WPW syndrome. At 3 months after RFA, patients showed significant improvement in both physical (13.5%) and mental (17.2%) health components; at 12 months, QoL parameters reached those of the controls. **(Int J Biomed. 2015;5(3):123-126.)**

Key words: *Wolff-Parkinson-White (WPW) syndrome; radiofrequency catheter ablation (RFA); quality of life; 36-Item Short-Form Health Survey.*

Introduction

Wolff-Parkinson-White (WPW) syndrome is one of several disorders of the conduction system of the heart that are commonly referred to as pre-excitation syndromes. It is characterized by paroxysmal atrioventricular re-entrant tachycardias (AVRT) with re-excitation of a region of cardiac tissue by a single impulse (re-entry) along an abnormal accessory conduction pathway between the atria and the ventricles [1]. In the general population the incidence of WPW syndrome is between 0.1% and 0.2%, which amounts to 4 cases per 100,000 of population a year. The prevalence of WPW syndrome has been estimated at 0.1 to 3.1/1000, occurring most frequently in young men; the male-to-female ratio is 3:2. As a rule, most patients (70%) have no signs of cardiovascular disorder [2,3]. In first degree relatives of patients with WPW syndrome, the frequency of this conduction disorder increases to 0.55%. The patients with the disorder in family history are at risk to have multiple accessory atrioventricular (AV) pathways [4]. Today, a study to determine a patient's QoL is regarded as a substantial, if not the basic, method for assessment of treatment efficacy in clinical settings. The purpose of the current study was to compare QoL scores in patients with WPW syndrome before and after the RFA procedure.

Methods

For the purpose of the study, we examined 60 patients (mean age 33.3±12.1 years, *Me* 32.0 years; IQR 23.8-39.0) diagnosed with WPW syndrome, 41(68.3%) men and 19(31.7%) women. Mean duration of arrhythmia in the patients' medical history was 6.57±4.43 years (*Me* 6.0 years; IQR 3.9-9.0). Twenty-eight apparently healthy persons (mean age 41.8±15.4 years, *Me* 43.0 years; IQR 31.5-56.5), 8(28.6%) men and 20(71.4%) women, without cardiovascular pathologies were included in the control group. Arterial hypertension and hypotension were diagnosed in 10(16.7%) and 11(18.3%) patients, respectively; 9(15.0%) patients had ischemic heart disease in their medical histories. To assess the patients' QoL, we used MOS 36-Item Short-Form Health Survey (MOS SF-36). The SF-36 is a measure of health status and is commonly used in health economics as a variable in the quality-adjusted life year calculation to determine the cost-effectiveness of a treatment. The SF-36 consists of 8 scaled scores, which are the

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weighted sums of the questions in their section. The 8 sections include physical functioning (PF), physical role functioning (or role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (or energy/fatigue) (VT), social role functioning (SF), emotional role functioning (or role limitations due to emotional problems (RE) and mental health (or psychological distress and psychological well-being) (MH).

Electrophysiology testing and radiofrequency catheter ablation

All patients who gave written consent to participate in the study in compliance with the World Medical Association Declaration of Helsinki received endocardial electrophysiology (EP) testing and RFA after withdrawal of antiarrhythmics for at least 6 half-lives. The study design was approved by commission of clinical trials at the Republican Specialized Center of Cardiology, Uzbekistan Public Health Ministry. Endocardial EP testing and the RFA procedure were performed routinely in one surgical intervention by means of the Elkart II EP system (Electropulse, Tomsk, the Russian Federation). The Seldinger technique was used to puncture the right jugular vein and left femoral vein under local anesthesia (40.0 ml of 0.5% solution of Novocain) for introduction of two electrode catheters into the heart cavity by means of introducers to perform EP testing and RFA in CS and RVa positions.

A 12-lead ECG to record baseline sinus rhythm in patients with WPW syndrome was followed by EP testing to localize an accessory AV pathway. At the accessory AV pathway localized around the tricuspid valve, the right femoral vein was punctured to introduce the ablation catheter into the heart cavity and to place it close to the pathway. During RFA (electrode temperature 50-55°C, power output 25W, electrode impedance 100-110 Ohm), electrophysiological criteria for the accessory conduction pathway's absence were registered. Retrograde trans-aortal access was used to perform the RFA for the left wall accessory AV pathway. The RFA procedure was followed by control standard EP testing. No antiarrhythmic post-operation therapy was prescribed.

All data was processed by means of a STATISTICA 6 and BIOSTAT software packet. Quantitative parameters are presented as M±SD as well as Median (*Me*) and 25th and 75th percentiles as Inter Quartile Range (IQR). Intergroup differences were considered significant at $P=0.05$.

Results

We have analyzed immediate and long-term outcomes of radiofrequency catheter ablation in 60 patients with WPW syndrome. Manifest, latent, and intermittent forms of WPW syndrome were found in 39(65.0%), 12(20.0%) and 9(15.0%) patients, respectively. Right and left accessory pathways were registered in 34(56.7%) and 26(43.3%) patients, respectively.

Other heart rhythm disorders were registered in 19(31.7%) patients with WPW syndrome: atrial fibrillation and atrial flutter were found in 14(23.3%) and 5(8.3%) patients, respectively.

At follow-up after 12 months, radiofrequency catheter ablation performed in patients with WPW syndrome was found effective in 93.3% (n=56). In 2(3.3%) patients RFA was inefficient due to deep localization of accessory conduction pathways and their proximity to the *His* bundle. In this group, due to complications RFA was inefficient in 2(3.3%) patients. In the first case, hemotamponade occurred due to perforation of the anterior wall of the right ventricle. Mobitz' type I atrioventricular block of second degree characterized by a progressive lengthening of the P-R intervals – identical to the Wenckebach phenomenon – occurred in one patient with a parahisial accessory pathway. The pericardial cavity was drained, and nonsurgical treatment was used to arrest bleeding. All patients were discharged from the Center in satisfactory condition in 3 to 4 days after RFA.

Physical Health Component

As compared with the controls, significant reduction in the physical functioning (PF) parameter (27.2%) could be seen in patients with WPW syndrome before RFA, indicating considerable restriction of the patients' physical activity. The mean physical component summary before RFA procedure was 46.6±6.09 (Table 1).

Table 1.

The SF-36 scores in patients with WPW syndrome (Physical Health)

Scales	Control	Before RFA	After RFA		
			3 months	6 months	12 months
Physical Functioning (PF)	76.0±8.8	55.3±13.4 P_1<0.0001	62.0±10.5 P_1<0.0001 P_2=0.003	69.3±10.4 P_1=0.004 P_2<0.0001	77.4±8.34 P_1=0.47 P_2<0.0001
Role-Physical (RP)	75.1±10.7	42.8±12.2 P_1<0.0001	53.3±8.65 P_1<0.0001 P_2<0.0001	63.6±10.7 P_1<0.0001 P_2<0.0001	68.4±9.83 P_1=0.005 P_2<0.0001
Bodily Pain (BP)	80.3±8.2	49.5±9.95 P_1<0.0001	54.6±8.74 P_1<0.0001 P_2=0.003	56.8±13.9 P_1<0.0001 P_2=0.001	71.1±9.19 P_1<0.0001 P_2<0.0001
General Health (GH)	81.1±9.4	48.4±8.86 P_1<0.0001	52.6±10.1 P_1<0.0001 P_2=0.02	58.3±13.2 P_1<0.0001 P_2<0.0001	72.4±8.76 P_1<0.0001 P_2<0.0001
Physical Component Summary	74.2±5.7	46.6±6.09 P_1<0.0001	52.9±4.05 P_1<0.0001 P_2<0.0001	58.9±5.89 P_1<0.0001 P_2<0.0001	68.7±4.13 P_1<0.0001 P_2<0.0001

P_1 – statistical significance vs control; P_2 – statistical significance vs before RFA

WPW syndrome was demonstrated to negatively affect the patients' everyday role functioning (RP), interfering with their personal and professional activity. The role functioning parameter was found to have decreased by 43% and the BP parameter by 38.4%, demonstrating a decrease in the patients' self-assessment of health (GH) by 40.3%. More than half of patients (n=35, 58.3%) pointed out that the threat of a

tachycardia episode restricted their performance of everyday routine activities, including housecleaning, unassisted shopping, stair climbing, and carrying heavy objects. At 3 months after RFA, we saw a significant increase in all parameters of QoL Physical Health Component, as compared with the pre-treatment values. Thus, PF, RP and BP parameters were found to increase by 12.1%, 24.5% and 10.3%, respectively; GH improved by 8.7%. The physical component summary was found to have increased by 13.5%. At 6 months after RFA, significant improvements could be seen in RP (48.6%), PF (24.3%), GH (20.5%) and BP (14.7%). After 12 months, a clear tendency to improvement was observed.

Mental Health Component

Analyzing mental health parameters before RFA, we could see a reduction in VT by 27.1% in patients with WPW syndrome. As compared with the controls, RE in patients with WPW syndrome was found to have decreased most of all (by 31.3%). The mental component summary was 57.6±12.1 (Table 2).

Table 2.

The SF-36 scores in patients with WPW syndrome (Mental Health)

Scales	Control	Before RFA	After RFA		
			3 months	6 months	12 months
Vitality (VT)	81.6±9.1	59.5±15.9 P_1<0.0001	69.3±11.9 P_1<0.0001 P_2<0.0001	81.6±15.2 P_1=0.99 P_2<0.0001	84.2±10.4 P_1=0.26 P_2<0.0001
Social Functioning (SF)	84.4±11.6	65.3±13.9 P_1<0.0001	73.8±12.2 P_1<0.0001 P_2<0.0001	76.7±12.7 P_1=0.008 P_2<0.0001	78.1±13.2 P_1=0.03 P_2<0.0001
Role-Emotional (RE)	82.0±10.3	56.3±15.3 P_1<0.0001	71.7±11.6 P_1<0.0001 P_2<0.0001	74.7±12.8 P_1=0.01 P_2<0.0001	77.6±13.8 P_1=0.14 P_2<0.0001
Mental Health (MH)	80.1±9.7	61.5±17.5 P_1<0.0001	69.4±11.1 P_1<0.0001 P_2=0.004	74.7±12.1 P_1=0.04 P_2<0.0001	76.9±14.2 P_1=0.28 P_2<0.0001
Mental Component Summary	77.9±5.3	57.6±12.1 P_1<0.0001	67.5±5.58 P_1<0.0001 P_2<0.0001	72.1±6.24 P_1<0.0001 P_2<0.0001	75.2±7.52 P_1=0.09 P_2<0.0001

P_1 – statistical significance vs control; P_2 – statistical significance vs before RFA

Before RFA, the MH and SF scores were found significantly lower in the patients than in the controls (by 23.2% and 22.6%, respectively). In our patients, 3 months after the RFA procedure all parameters of the mental health component were significantly increased as compared with those before treatment. As compared with the scores before RFA, VT and SF parameters increased by 16.5% and 13.0%, respectively. Improvement in RE and MH scores versus pre-RFA ones could be seen as well (by 27.4% and 12.8%, respectively). The mental component summary was found to have increased by 17.2%. At 12 months after RFA, our patients with WPW syndrome demonstrated significant improvement in their QoL; values of all mental health component parameters reached those among the controls.

Discussion

In patients with WPW syndrome, the physical component rather than the mental one seems to be responsible for the decrease in quality of life. We believe that low QoL scores in the patients with WPW syndrome before RFA procedure are associated with anxiety about their physical and emotional conditions caused by episodes of tachycardia. The patients perceived palpitations and heart flutter as well as arrhythmia attacks, which start and finish abruptly as barriers to a meaningful productive life. Almost half of the patients (n=29/48.3%) evaluated their own performance as inferior and less careful, and they thought that the volume and quality of their work decreased. The majority of patients with WPW syndrome have neither congenital nor acquired heart diseases. The physical and emotional conditions of patients with WPW syndrome, coupled with atrial fibrillation or atrial flutter, significantly affect their social activity and everyday role functioning. Revishvili et al. [5] reported that physical and mental health parameters in patients with atrial fibrillation decreased twofold as compared with those in healthy subjects. In our study, QoL physical and mental parameters were significantly lower in patients with atrial fibrillation.

Patients with WPW syndrome exhibit a wide spectrum of arrhythmias, including both ventricular and supraventricular ones, differently affecting hemodynamics. Re-entrant arrhythmias (orthodromic and antidromic tachycardias) occur in more than 70% of cases, negatively affecting patients' quality of life [6]. Some authors believe that changes in QoL parameters in patients with cardiovascular disorders are primarily governed by physical working capacity; reduction in the parameter can impede a patient's needs being met [7-9].

Conclusion

Radiofrequency catheter ablation was found effective in 93.3% of patients with WPW syndrome. At 3 months after RFA, patients showed significant improvement in both physical (13.5%) and mental (17.2%) health components; at 12 months, QoL parameters reached those of the controls.

Competing interests

The authors declare that they have no competing interests.

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Arteriovenous Relationships in the Pathogenesis of Encephalopathy

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Abstract

The study aims at investigating the disturbance in intra- and extracranial interaction of arterial and venous vessels in stable arterial hypertension (SAH) and building a model of vascular relationships in the system: inflow – the exchange field of cerebral blood flow – outflow. Baseline data were obtained by catheterization through a probe that was wedged in the superior bulb of the internal jugular vein, where the hemodynamic and biochemical parameters of cerebral blood flow were obtained. Arterial blood was collected from the thoracic aorta. We performed the correlation and factor analyses of the relationship between the parameters of inflow and outflow to the skull in SAH patients compared with those in the control group. The identified differences led to the following conclusions: There is a loss of homeostatic control for the hemodynamic (extra- and intracerebral) and biochemical regulation in SAH; the high-energy processes of the aortic chamber (systolic and pulse pressure) spread to the bloodstream of the brain; the damping function of carotid siphons is impaired; cerebral venous stasis is formed; increased pressure in the microvascular venous network of the brain is defined; and a loss of the homeostatic control of the rheological properties of blood is defined. The loss of extracranial regulation of intracranial venous pressure in SAH leads to venous plethora of the intracerebral vessels, increasing the "booster" pressure in the microvasculature, and circulatory hypoxia of brain tissues. The consequences of these changes are metabolic and hemodynamic disturbances in energy supply for activated neurons, as well as circulatory hypoxia resulting in disturbances of the regulatory function of the nervous system and mental activity, and the development of hypertonic angioencephalopathy. **(Int J Biomed. 2015;5(3):127-131.)**

Keywords: *cerebral venous stasis; circulatory hypoxia; homeostatic control; hypertonic angioencephalopathy.*

Abbreviations: **Ao**, aorta; **BP**, blood pressure; **CO**, cardiac output; **CBF**, cerebral blood flow; **CASs,** carotid artery siphons; **DP**, diastolic pressure; **EDP**, end-diastolic pressure; **HAE,** hypertonic angioencephalopathy; **IJV**, internal jugular vein; **IVP**, intracranial venous pressure; **LV**, left ventricle; **M,** mean value; **m,** confidence interval ratio; **MP**, mean pressure; **PP**, pulse pressure; **RV**, right ventricle; **RA**, right atrium; **SS**, sigmoid sinus; **SP**, systolic pressure; **SAH**, stable arterial hypertension; **SV**, stroke volume.

Introduction

The study of the relationships of the intracranial venous pressure with systemic arterial pressure and central aortic pressure in stable arterial hypertension (SAH), compared to the norm, is a main issue of this work. We built a model of the impact of the intracranial and cerebral blood flow on the development of disturbances in neuron activity and hypertonic angioencephalopathy (HAE) formation. Despite the importance of the problem, there are a small number of studies dedicated to impairments in the cerebral venous system in HAE. There is no consensus about the primary or secondary nature of venous pathology in arterial hypertension. Modern concepts of HAE pathogenesis mainly associate the clinical manifestations with the active processes in the arterial vascular bed. In particular, ischemic attack, "small" strokes, and progressive cerebral ischemia are considered as the main causes of HAE. There is a great deal of literature dedicated to changes in the structure and functions of intra- and extracerebral arteries and only a few studies dedicated to the role of the cerebral venous vascular bed in the development of HAE. In one such study, B. Mashsin et al have found a brain venous hemodynamic abnormality with an increase in blood flow volume and decrease in venous velocity, as well as an increase of the linear velocity in the arterial flow [1].

The purpose of this study was to create a model of

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relationships between the intracranial/cerebral arterial and venous flows both among themselves and with the systemic systolic pressure and central aortic pressure, and create a central concept of HAE pathogenesis, taking into account the abnormalities of the metabolic support for the actualized neural networks and related changes in the mental sphere.

Methods and Results

For all participants, the study was conducted in the same laboratory by the same methods. The data were obtained from patients in the supine position by catheterization through a probe that was wedged in the upper bulb of the internal jugular vein (IJV). The results indicate the levels of blood pressure (BP) in the venous system of the brain and sigmoid sinus (SS) (Tables 1 and 2).

Table 1.

Pressure levels (mmHg) in SS (IVP)

		SP	DP	PP	MP
Norm	M	10.5	8.3	2.4	9.4
	m	2.2	1.8	0.75	2.2
	Max	21	16.8	4.2	18.9
	Min	6	3.9	0.5	4.9
HAE	M	11.5	7.7	3.8	10.1
	m	3.2	2.9	1.4	3.9
	Max	22.6	19.2	7	20.4
	Min	3.9	2.1	1.3	2.4

Table 2.

Pressure levels (mmHg) in IJV

		SP	DP	PP	MP
Norm	M	7.3	5.5	2.1	6.7
	m	1.1	1	0.6	1.3
	Max	13.8	10.5	5.1	11.7
	Min	2.4	2	0.2	1.4
HAE	M	8.7	6.3	2.6	7.2
	m	3.4	3.3	1.1	3.2
	Max	21	14.	6.4	15.7
	Min	2.4	0.5	1.2	2.1

Catheterization was performed by percutaneous puncture of the right femoral artery and the right femoral vein using the Seldinger technique. BP was recorded in the thoracic aorta. The study was conducted under X-ray control. We evaluated the results obtained in patients with essential hypertension grade 2 and resistant to therapy. Since preliminary analysis showed no significant differences among patients, we considered the study group as a homogeneous group with SAH. The study included 61 patients. To compare the results, data of 60 people in the control group were obtained and processed by methods of mathematical statistics in a similar way. The detailed description of the groups and methods of the results processing were shown previously [2]. For intracranial venous pressure (IVP) in SAH, we note despite being within the boundaries of the "zone of norm," a reliable growth of pressure level (by 8% to 9%), especially significant for the pulse pressure (by 58%). Presence of the pressure gradient between the intra- and extracranial venous systems, despite the varying levels of pressure in the IJV (the effect of intrathoracic and barometric pressure), proves that IVP is formed with the participation of the factors affecting in IJV. Previously [6], we have observed a radical change in the composition and quality of the correlations for intra- and extracranial blood flow with other parameters in SAH. Particularly important are the loss or inversion of correlations with the parameters of general and plasma viscosity and rheology, as well as the loss of correlations with the final gas exchange products of the brain that determine the plasma gas tension (O_2, CO_2).

All levels of pressure in the right atrium (RA) in SAH (out MP) significantly exceed the boundaries of the normal zone (Table 3). Pressure levels in Ao and LV are shown in Table 4.

Table 3.

Pressure levels (mmHg) in RA

		RA					LV	
		A	X	V	Y	MP	EDP	MP
Norm	M	5.7	2.4	4.6	3.4	4.1	5.1	14.4
	m	0.9	0.7	0.8	0.2	1.1	1.2	1.8
	Max	8.8	5.3	6.5	6.0	8.4	10	19.8
	Min	3.0	0	1.6	0	1.2	0	8.8
HAE	M	7.4	4.0	6.4	4.7	3.4	3.4	13.9
	m	2.7	2.1	2.8	2.0	2.6	2.6	4.4
	Max	11.8	9.0	14.1	9.0	8.4	8.4	28
	Min	1.8	0	1.8	0	0	0	6.6

Table 4.

Pressure levels (mmHg) in Ao and LV

		CO	SV	Ao				LV	
				SP	DP	PP	MP	SP	PP
Norm	M	10.9	128.4	114	71	40.3	92.6	108	100.5
	m	1.3	22.4	4.5	3.8	3.5	5.1	6.4	7.1
	Max	18.7	186	147	87	65	115	130	130
	Min	5.5	80	90	50	21	70	90	85
HAE	M	11.1	147	180	101	79	137	180	168
	m	3.1	38,9	31	21	22	23	34	28
	Max	21.7	246	270	155	144	210	260	248
	Min	5.3	50	150	78	40	96	150	138

Previously, we analyzed correlations between parameters of RA pressure and indicators of IVP, as well as

between the biochemical parameters (including rheological parameters) of blood flowing from the brain [6]. We found a loss of correlations for pressure among the parameters of general and plasma viscosity, vasoactive regulators of cerebral blood flow (electrolytes), and final metabolites of the brain (arteriovenous difference in O_2 and HbO_2) in SAH. In other words, during development of SAH there is a loss of regulatory relationships of the RA and IVP with brain metabolites and rheological parameters in a single hemodynamical chamber (IVP--RA), where the main regulator, in our opinion, is the minimal pressure in the outflow tract from the brain: in the RA. These data are well known and shown for complete characterization of the study issue. In norm, the active process of the left ventricle (LV) systole (systolic and pulse pressure in aorta (Ao) and LV) have no correlations with the pulse pressure (PP) in SS (Table 5). LV systolic and pulse pressures are in negative association with systolic, diastolic and mean pressure of SS. Consequently, the formation of IVP in norm does not depend on Ao PP, at the same time it has a relationship with the systolic, diastolic and mean pressure in Ao. In SAH, there is a loss of the correlation between IVP and the pressure in the aortic chamber, but a correlation between the active phase of LV and SS PP is found. Thus, in norm, IVP levels correlate with the LV ejection phase; maximum of pressure in system VS--Ao is achieved with opening of the aortic valve; maximal pressure for the skull (brain) is formed; a wave process in Ao (immediate application area is extra- and intracranial blood vessels) is generated.

Table 5.

Correlations between IVP and Ao - LV

	IVP	Ao				CO	LV	
		SP	DP	PP	MP		SP	PP
Norm	SP				+	-	-	-
	DP		+		+	-	-	-
	PP		-					
	MP				+	-	-	-
HAE	SP			+				
	DP							
	PP	+	+	+	+		+	
	MP	-	-		-			

In the horizontal position, LV systole, forming a rotational and translational movement around the outer (variable) axis in the form of a spherical wave structure [3] of aortic flow, reaches all areas of the body before closing the aortic valve [4]. The negative correlation with the levels of IVP is explained only by the existence of a characteristic structure between the cavity of the skull and extracranial vessels, which changes its clearance under the influence of the wave process. We believe that this structure is carotid artery siphons (CASs) located in the cavernous sinus. CASs are guides for wave structures of the heart; they are informative characteristics of different levels of regulation [2] interfering in the cavernous sinuses of the dura mater.

The presence of CASs explains the negative relations between the IVP and LV ejection phase in norm. This relation changes diametrically in SAH and becomes positive, which indicates parallel changes in IVP and Ao pressure, which are possible only as a result of changes of functional relationships in the system CASs--cavernous sinus which is connected through the *sinus petrosi inferior* with the zone of catheter wedging while obtaining the initial data. It should be also noted that the sympathetic plexus of CASs participates in innervations of the eyeball, which plays an important role in purposeful behavior. The increased IVP in SAH is necessary to maintain the pressure gradient at the required level to ensure the adequate perfusion and cerebral metabolic processes (in the zone of norm). This is possible only if the ability to the extracranial regulation (the defeated CASs) is lost, as well as the lesion of the intracranial vascular bed with narrowing of the lumen and rigidity of vascular wall.

We consider the phase of aortic peak during Ao and LV separation as 1) a final stage of the high-energy phase and 2) an initial stage of the diastolic evolution. The action of CASs, whose contraction is caused by LV systole, makes a "selection" (damping) of the pressure, starting with a value equal to the average BP. Pressure levels exceeding the average BP in norm remain in "reserve" to respond in stressful situations (in principle, it is quite a minimal adaptive response, namely, the diminution of CAS reaction to the aortic wave process). First of all, the average BP is positively associated with ICP up to diastolic BP, which indicates the setting of the unified hydrodynamic system (Ao - vessels entering the skull - IVP) in the phase of the diastolic evolution (from average to diastolic pressure). This explains the positive relationship of the diastolic evolution of the intracranial venous bed with the aortic diastolic evolution. Achieving minimal values by the Ao–IVP gradient is replaced by the LV systole. In other words, Ao pressure--IVP relationships change their own correlation from the negative through "zero" to the positive during one cardiac cycle. The radical difference for SAH is: 1) the dependence of IVP only on the high-energy phase with an inversion of direction of regulation; 2) the lack of correlation at all stages of the diastolic evolution; 3) the lack of a reserve of pressure for urgent adaptation. Thus, during SAH development, despite the increase in energy expenditure to ensure the cerebral blood flow and metabolism, the efficiency of metabolic support for the brain functioning is reduced. Our data [2] suggest that during SAH development, there is a loss of the hemodynamic mechanisms for correction of the negative manifestations of hyperfibrinogenemia, rheological and viscous blood parameters, and thrombus formation; ie, there is a loss of regulation of conjugation between thrombotic factors and pressure towards the outflow from the brain, both of which exist in norm. Pathways of the venous outflow according to the pressure gradient from the cortex through the venous sinuses in the RA have no valves, making a unified hemodynamic chamber [2]. The pressure at the outlet of the intracerebral venous bed in the zone of minimal pressure significantly increases the entire range of values in SAH. The critical value for intravascular pressure in veins depends on the ratio of wall thickness to the radius of the vessel and elastic

modulus. Loss of stability and a sharp change in the lumen of the intracranial veins occurs at pressure changes by 0.2 to 0.5 Hg, resulting in a change in the throughput volume capability and the cross-sectional shapes of venules and veins. A gradient of transmural pressure effects in the system "liquor--veins" is possible in both directions, and an increase in venous pressure, causing the maximal volume flow, increases the transmission pressure on the liquor. The decreased venous blood flow, which is accompanied by liquor hypertension, is found in SAH. The increase in venous stasis is a marker of decompensation of cerebral circulation. A disparity between the rate of arterial inflow and venous return (delay) is more pronounced in patients with chronic heart failure [5]. We believe that in a unified hydrodynamic chamber with the outflow according to the pressure gradient, the disturbances in any portion of unified hemodynamic space "intracerebral veins--RA" [2] affect the condition and regulation of the entire intra- and extracerebral venous flow regardless of the exposure vector (along or against the blood flow). Increasing the "booster" venous pressure in the valveless bloodstream inevitably leads to increased pressure in the main outflow tracts from the brain ((1) superior sagittal sinus - bridging veins - cortical cuff - cortical veins, (2) straight sinus - deep cerebral veins -cortical veins) against the blood flow to the functional unit of the microvasculature network: post-capillary venule—capillary—pre-capillary arterioles. The increase in the "booster" venous pressure according to the previously described mechanism [6] is spread through valveless veins on the entire volume of the brain, and affects the liquor pressure in accordance with the transfer mechanism.

The minimum dimensions of the neural structures, in which there are the marked changes in blood flow (functional hyperemia--FH) under functional load, correspond to the size of neural columns. According to G. Mchedlishvili [7], the initial stage of FH has neurogenic regulation, but the K/Na pump having the mechanisms of metabolic supply for neurons has almost the same time parameters. During development of the activity in the exchange field of the actualized neural network (the excited neurons), the venous vessels eliminating metabolites are already in a state of maximum volumetric capacity without the possibility to remove the additional blood volume by changing the volume of the venous vessels.

The decreased rate of blood flow in the microvasculature cannot be compensated for by a Fareusa-Lindqvist effect. Additional complicating factors of blood flow in the macro- and microcirculation networks are disorders in aggregation, rheology and viscosity properties of blood with the loss of homeostatic control, and loss of regulation of the hemodynamic and biochemical interactions, which take place in norm [2]. All of this results in a delay in metabolite elimination, O_2 deficiency, an excess of CO_2, a lack of glucose, changes in intra- and extravascular concentration of electrolytes (regardless of the activity of transmembrane channels), increased platelet activity, and other abnormal reactions (ie, all of the above are indicators of the development of local circulatory hypoxia). Disturbances in the metabolism of neurons, which occur due to the lack of substrates for oxidation, lead to a reduced formation of macroergic substances (ATP, ADP, creatine phosphate). Accumulation of metabolites is a disturbing factor. Thus, with an increase in the activity of neurons and formation of activated neural associations, there is a local circulatory hypoxia. Manifestations of circulatory hypoxia are the changes in activity of selective channels of membranes, and in their permeability (especially for Na, K, and Ca) and excitability, and destruction of structural patterns of neurons (nucleus, organelles, and cytoplasm). The excess of the oxidized metabolites plays a special role in damaging cellular and intracellular membranes. A result of this excess is characterized by the development and progression of degenerative processes in neurons, impaired intracellular signaling (both in neurons and the adjustable effector cells), a change of phosphorylation and the activity of functional proteins. Many researchers characterize the disturbances in the energy supply of K/Na, Ca membrane pumps leading to abnormalities in the transmembrane gradient of electrolyte concentrations as one of the main mechanisms of neuronal hypoxia. These disturbances lead to membrane depolarization and inactivation of the transmembrane channels. Abnormalities in the calcium pump reduce Ca release from cytosol to the extracellular environment with deposition in endoplasmic reticulum. There is a reduction of FH in the projection area of the conditioned response caused by a decrease in the blood supply to the cortex in SAH [8]. The total result of the above-described is a disturbance of the integrative activity of the nervous system in different forms: the pathological determinants, the pathological dominants, the pathological systems and others [9], as well as the suppression of neuronal population activity [10].

In hypoxic changes of cortex, hyperexcitability (a decreased threshold) and metabolic acidosis, the sensory stimulus for activation and the subsequent activity of neural networks have a lower (compared with the norm) power and duration of the signal for initiating the operation of the "answer" mechanism and metabolic supply for the exchange fields of the involved neurons. The reduced energy level of the initial signal means an increase in the total amount of information and the range of the readable signals from the environment.

The increase in size of the information field and excessive sensory stimulation (as a consequence) associated with difficulty in selecting the main control signal leads to excessive stimulation of the synapses of the afferent impulses and changes in the efficiency of synaptic transmission in the form of long-term potentiation and depression (pathological excitation or inhibition). Abnormalities in the allocation of the main control signals lead to the deficit model of reality distortion and the disturbance of translational symmetry. Formation of an objective reality model having an information deficit and mismatch leads to discrepancies in the projection mechanisms to the real parameters of the environment, as well as disturbances of the adequacy and determinism in the system "environment – man – environment." Projection is a way of interacting, adapting, and searching for methods to maintain homeostatic equilibrium ("Deterministic equivalent response" according to Le Chatelier). Having a structural mismatch to the original information field (objective reality)

the "projection" (cognitive product) is not equivalent, but rather asymmetric, to the content of the external world, with a growing parametric discrepancy. The consequence of this is: an increasing mismatch in stimulus-response; stereotyping of behavioral forms (the result of the stable existence of neural associations of standard answer); a decrease in the adaptive arsenal; and adjustment disorder (physiological, psychological, and social).

Conclusion

There is a loss of homeostatic control for the hemodynamic (extra- and intracerebral) and biochemical regulation in SAH; the damping function of carotid siphons is impaired; the high-energy processes of the aortic chamber (systolic and pulse pressure) spread to the bloodstream of the brain; cerebral venous stasis is formed; increased pressure in the microvascular network of the brain is defined; and a loss of the homeostatic control of the rheological properties of blood is defined. The loss of extracranial regulation of intracranial venous pressure in SAH leads to venous plethora of the intracerebral vessels, increasing the "booster" pressure in the microvasculature, and circulatory hypoxia of brain tissues. The consequences of these changes are metabolic and hemodynamic disturbances in energy supply for activated neurons, as well as circulatory hypoxia resulting in disturbances of the regulatory function of the nervous system and mental activity, and the development of HAE.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

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Alpha-Adducin Gly460Trp Polymorphism and Clinical Efficacy of Indapamide in Uzbek Hypertensive Patients

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Abstract

The purpose of the present study was to evaluate pharmacogenetic aspects of the antihypertensive, cardioprotective and vasoprotective efficacy of Indapamide in association with the ADD1 Gly460Trp polymorphism in Uzbek hypertensive patients.

Materials and Methods: The study included 37 ethnic Uzbek patients (mean age of 47.14±9.54 years) with untreated Hypertension (HT) of Grade 1 and 2 (ESH/ESC, 2013) and average HT duration of 5.7±4.33 years. All patients underwent clinical examination, echocardiography, Doppler sonography study, assessment of flow-mediated dilation (FMD) of the brachial artery and microalbuminuria (MAU) in daily urine. Genomic DNA was extracted from peripheral blood using the Diatom™ DNA Prep 200 Kit according to the manufacturer's protocol. The PCR-RFLP technique with visualization was performed to determine the ADD1 Gly460Trp polymorphism. Indapamide was prescribed as monotherapy for 12 weeks with an initial dose of 2.5 mg.

Results: A 12-week monotherapy with Indapamide in a daily dose of 2.5 mg showed the high antihypertensive efficacy of this drug expressing a reliable decrease in absolute values of SBP and DBP independently as carrying of the ADD1 Gly460Trp polymorphism allele. Positive changes in LVM during therapy in patients of both allele groups were accompanied by an improvement in LV diastolic function with significant positive dynamics of IRP. The target normalization of FMD was achieved only in the presence of Gly-allele, as well as a significant decrease in IMT and MAU during treatment.

Conclusion: The results of our study showed high antihypertensive and cardioprotective efficacy of Indapamide treatment independently on carrying of the ADD1 Gly460Trp polymorphism. At the same time, we revealed certain advantages in the vasoprotective efficacy of Indapamide treatment in Uzbek hypertensive patients who are carriers of Gly-allele of the ADD1 Gly460Trp polymorphism. **(Int J Biomed. 2015;5(3):132-136.)**

Keywords: *hypertension; Indapamide; alpha-adducin Gly460Trp polymorphism.*

Abbreviations: BP, blood pressure; **LVEDD**, left ventricular end-diastolic dimension; **LVESD**, left ventricular end-systolic dimension; **IVST**, interventricular septal thickness; **PWT**, posterior wall thickness; **LVMI**, left ventricular mass index; **PE**, peak early filling velocity; **PA**, peak atria1 filling velocity; **IRP**, isovolumic relaxation phase; **IMT**, intima-media thickness; **FMD**, flow-mediated dilation; **MAU**, microalbuminuria.

Introduction

Hypertension (HT) is a main risk factor for cardiovascular mortality. Currently, HT control is the most significant way to reduce cardiovascular risk [1-5]. However, different approaches exist in the choice of antihypertensive drugs. Individual response to antihypertensive therapy, as well as the spectrum of unwanted side effects, promotes poor adherence to treatment. The variability in drug response is of great interest for pharmacogenetic studies. The HT treatment should start with thiazide diuretics in accordance with guidelines for the management of HT (ESC/ESH, 2013). Indapamide has a special place among diuretics due to its high efficacy, a good tolerability, and metabolic neutrality [6-9]. About 60% to 70% percent of indapamide is eliminated through the kidneys. Sodium retention remains the cornerstone of the pathogenesis and the treatment of HT, and thiazide diuretics remain as drugs of choice in treatment of hypertensive patients in the general population [1]. Nevertheless, not all hypertensive patients are salt-sensitive, and patient response to sodium retention and diuretics is variable [10-11].

Adducin is a heterodimeric cytoskeleton protein

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comprising either alpha/beta or alpha/gamma heterodimers. Its subunits are encoded by 3 related genes (ADD1, ADD2, and ADD3, which show alternative spliced variants) located on different chromosomes [12]. The α-subunit is known to increase renal sodium reabsorption and may be involved in the pathophysiology of essential hypertension. The human ADD1 gene is located on chromosome 4p16.3 and comprises 16 exons [13]. ADD1 gene is considered as a major candidate gene for AH. One of the well-studied polymorphisms in the ADD1 gene is a substitution of Gly for Trp at amino acid residue 460 (G460W, rs4961). In clinical studies, some have reproduced the supportive association between Gly460Trp polymorphism and AH or BP level [14-17], whereas others were unable to replicate these findings [18-22].

The ADD1 Gly460Trp polymorphism, C825T polymorphism of the GNB3 gene, and β-T594M polymorphism of the epithelial sodium channel gene are genetic markers associated with expression of albumens that are connected with renal sodium transport. Of these polymorphisms, the ADD1 Gly460Trp polymorphism has the biggest influence on the relationship between the efficacy of diuretics treatment and sodium sensitivity.

The aim of this study was to evaluate pharmacogenetic aspects of the antihypertensive, cardioprotective and vasoprotective efficacy of Indapamide (Indap, Pro.Med.CS, Czech Republic) in association with the ADD1 Gly460Trp polymorphism in Uzbek hypertensive patients.

Materials and Methods

The study included 37 ethnic Uzbek patients (mean age of 47.14±9.54 years) with untreated HT of Grade 1 and 2 (ESH/ESC, 2013) and average HT duration of 5.7±4.33 years. The study was approved by the Republican Specialized Center of Cardiology Ethics Committee. Written informed consent was obtained from each patient. The diagnosis of HT was based on 2013 ESH/ESC Guidelines for the management of arterial hypertension [3]. Exclusion criteria were symptomatic hypertension, clinical evidence of cerebrovascular or coronary heart diseases, cardiac arrhythmia, heart failure, renal impairment, diabetes mellitus, metabolic and other background diseases, alcohol intake greater than 30g of pure ethanol per day, and smoking.

Echocardiography and Doppler sonography study carried out on the unit «EnVisorC®» by standard methods using the recommendations of the American Society of echocardiography (Sahn DJ, Demaria A, 1987) The following parameters were measured and calculated: IVST, PWT, LVEDD, LVESD, EF, LVEVD, LVESV, and LVM (LVM was calculated using the formula R. Devereux (1977). LVM was indexed to body surface area (LVMI). Left ventricular hypertrophy (LVH) was defined as LVMI of >95 g/m^2 (for women) and >115 g/m^2 (for men).

The ratio of peak early filling velocity to peak atria1 filling velocity (PE/PA) was calculated. The isovolumic relaxation phase (IRP) was also measured.

Carotid artery intima-media thickness (IMT) was measured by a 7.5 MHz high-resolution ultrasound (EnVisorC®). IMT was defined as maximum thickness of IMT at the region of interest detected in both left and right carotid artery including common carotid artery.

Assessment of flow-mediated dilation (FMD) of the brachial artery has been used as a method of determining endothelial function. The diameter of the brachial artery was measured from two dimensional ultrasound images, with the 7.5 MHz linear array transducer and standard EnVisorC® system. In each study, scans were taken at rest and during reactive hyperemia. FMD was estimated as the percent change in the diameter relative to the baseline diameter at rest. Level of FMD≥10% was taken as the norm threshold based on the Celemajer works [24].

The degree of microalbuminuria (MAU) in daily urine was determined with enzymatic method using biochemical analyzer ("Daytona TM", «Rendox», UK), which allows evaluate the MAU within 20-100 mg/l and above.

Genomic DNA was extracted from peripheral blood using the Diatom™ DNA Prep 200 Kit according to the manufacturer's protocol. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique with visualization was performed according to previously described methodologies to determine the ADD1 Gly460Trp polymorphism [23].

Indapamide was prescribed as monotherapy for 12 weeks with an initial dose of 2.5 mg.

Statistical analysis was performed using the statistical software «Statistica» (v6.0, StatSoft, USA). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±SD for continuous variables. Student's unpaired and paired t-tests were used to compare two groups for data with normal distribution. Deviation from Hardy-Weinberg equilibrium and differences in allele distributions between the two groups were assessed by χ2- test with 1 degree of freedom (df). Two-tailed *P* values *<0.05* were considered statistically significant.

Results

Distribution of alleles of ADD1 Gly460Trp polymorphism in patients was similar to our early study [25]. In particular, among hypertensive patients (n=160) Gly-allele was revealed in 76.9% of cases, and Trp-allele in 23.1% of cases (χ^2=182.75, df=1, *P=0.000*); herewith, in normotensive subjects (n=58) the Gly and Trp allele frequency was 71.6% and 28.4%, respectively (χ^2=41.39, df=1, *P=0.000* [25]). The significant accumulation of Gly-allele of the ADD1 Gly460Trp polymorphism was shown. The allele frequency did not differ significantly between the hypertensive and normotensive subjects. Due to the small number of patients subjected to 12-week indapamide treatment, only allele analysis of antihypertensive and antiremodeling efficacy was performed. Patients were divided into two groups: Group 1 – Gly-allele carriers (n=53) and Group 2 – Trp-allele carriers (n=21), 71.6% and 28.4%, respectively (χ^2=29.973, df=1, *P=0.000*). According to the initial level of BP and the initial parameters of LVH and ED, the Gly and Trp allele carriers of ADD1 Gly460Trp polymorphism were not different from each other.

Estimation of antihypertensive efficacy of Indapamide

A 12-week monotherapy with indapamide in a daily dose of 2.5 mg showed the high antihypertensive efficacy of this drug expressing a reliable decrease in absolute values of SBP and DBP independently as carrying of the ADD1 Gly460Trp polymorphism allele (Table 1). In two study groups, the high level of BP reduction estimated by the degree of reduction in mean blood pressure >10% (-18.2±5.9% for Group 1 and -16.4±4.7% for Group 2) was noted. Positive antihypertensive efficacy was noted in 92.5% of cases for Group 1 and 90.5% cases for Group 2. Achievement of the target level of SBP was noted in 83% of cases for Group 1 and 95.2% of cases for Group 2 (χ^2=1.382, df=1, *P=0.240*). Achievement of the target level of DBP was noted in 83% of cases for Group 1 and 90.5% of cases for Group 2 (χ^2=0.401, df=1, *P=0.526*). Simultaneous achievement of target levels of SBP and DBP was noted in 75.5% of cases in Group 1 and 85.7% of cases in Group 2. It is possible to note a certain tendency towards a better antihypertensive response in patients with Trp-allele of the ADD1 Gly460Trp polymorphism.

Table 1.

Antihypertensive efficacy of 12-week monotherapy with Indapamide in association with the ADD1 Gly460Trp polymorphism

Variable	Group 1	Group 2
SBP, mmHg	151.79±11.6 124.62±10.04*	149.3±7.46 125.95±7.52*
DBP, mmHg	96.6±8.25 78.5±7.94*	94.29±6.57 78.1±7.15*
Mean BP, mmHg	115.0±8.22 93.87±7.63*	112.62±6.25 94.05±5.76*
SBP, Δ%	-17.8±5.4	-15.6±4.3
DBP, Δ%	-18.4±8.8	-16.96±7.8
Mean BP, Δ%	-18.2±5.9	-16.4±4.7
Achievement of target levels of SBP,% DBP,%	 83% 83%	 95.2% 90.5%
Achievement of target levels of SBP and DBP,%	 75.5%	 85.7%

*Note: *- P<0.001 between before and after treatment; numerator – before, denominator – after treatment.*

Estimation of cardioprotective efficacy of Indapamide

Our analysis revealed no certain advantages of antiremodeling therapy depending on the allelic carrier (Table 2). A significant decrease in IVST and PWT was shown in two study groups. We revealed no differences in degree of IVST and PWT reduction: -5.37±6.93% vs. -6.05±7.98% (*P>0.05*) for IVST in Groups 1 and 2, respectively; -7.79±7.91% vs. -5.06±8.78% (*P>0.05*) for PWT in Groups 1 and 2, respectively. The revealed dynamics of LV wall thickness were accompanied by a significant regression of LVM (Table 2); the degree of LVMI reduction was -13.4±9.5% in Group 1 and -10.9±9.4% in Group 2 (*P>0.05*). A significant reduction of LVM in carriers of Gly-allele during indapamide therapy was associated with a reduction in the degree of the concentric LVH. It should be noted that only Group 1 patients showed a significant increase in the EDV/LVM ratio: 0.63±0.10 ml/g before treatment and 0.69±0.10 ml/g after treatment (*P<0.02*) compared to Group 2 patients: 0.63±0.13 ml/g before treatment and 0.68±0.14 ml/g after treatment (*P>0.05*). Such positive changes in LVM during therapy in patients of both groups were accompanied by an improvement in LV diastolic function with significant positive dynamics of IRP.

Table 2.

Cardioprotective efficacy of 12-week monotherapy with Indapamide in association with the ADD1 Gly460Trp polymorphism

Variable	Group 1	Group 2
IVST, cm	1.05±0.13 0.96±0.12***	1.06±0.15 1.01±0.15**
PWT, cm	0.88±0.14 0.83±0.12*	0.91±0.22 0.85±0.22**
EDV/LVM, ml/g	0.63±0.10 0.69±0.10**	0.63±0.13 0.68±0.14
EDD, cm	5.55±0.49 5.41±0.50	5.66±0.36 5.54±0.34
ESD, cm	3.37±0.34 3.29±0.36	3.44±0.25 3.36±0.25
EF, %	69.20±3.29 68.86±3.84	68.94±3.43 69.20±3.75
PE/PA	1.04±0.31 1.03±0.24	1.06±0.30 1.10±0.27
IRP, sec	0.100±0.02 0.092±0.02*	0.100±0.01 0.085±0.03*
LVM, g	247.47±62.70 213.77±53.20**	263.24±67.43 235.2±72.17***
LVMI, g/m²	124.77±26.01 107.70±22.49***	132.19±29.22 117.8±30.57***
IVST, Δ%	-5.37±6.93	-6.05±7.98
PWT, Δ%	-7.79±7.91	-5.06±8.78
LVMI, Δ%	-13.4±9.5	-10.9±9.4

*Note. *- P<0.05, **- P<0.02, ***- P<0.001 -- between before and after treatment; numerator – before, denominator – after treatment.*

Estimation of vasoprotective efficacy of Indapamide

The analysis of the vasoprotective efficacy of Indapamide (Table 3) by the dynamics of FMD, IMT, and MAU testified to the drug's benefits in Group 1 patients. In particular, on the background of positive dynamics of FMD in patients of both groups, the target normalization of FMD was achieved only in the presence of Gly-allele (10.60±4.19%). Only in Group 1 patients did we find a significant decrease in IMT and MAU during treatment (Table 3).

Table 3.

Vasoprotective efficacy of 12-week monotherapy with Indapamide in association with the ADD1 Gly460Trp polymorphism

Variable	Group 1	Group 3
D, Δ%	9.47±3.91 10.60±4.19	8.85±4.14 9.73±3.61
MAU, mg/l	16.11±18.73 7.86±5.94**	13.83±8.05 10.05±10.12
IMT, mm	0.86±0.15 0.80±0.16*	0.86±0.20 0.82±0.15
MAU, Δ%	-30.54±40.58	-8.86±101.4

*Note. *- P<0.05, **- P<0.001 -- between before and after treatment; numerator – before, denominator – after treatment.*

Discussion

In the current study, we present the results of the pharmacogenetic features of Indapamide in association with the ADD1 Gly460Trp polymorphism in Uzbek hypertensive patients.

D. Cusi et al. [14] first identified the Gly460Trp polymorphism and showed the increased response to a decrease in serum sodium and diuretic therapy in hypertensive patients who were the 460Trp-allele carriers [14]. Subsequent studies have found an increased pressure response to salt load in carriers of the 460Trp-allele suffering from HT compared to Gly/Gly-homozygous HT individuals [26]. In two additional studies of the same research group, the significantly greater antihypertensive response to hydrochlorothiazide was found among the 460Trp-allele carriers [27,28]. In the study of Grant and others, a significantly greater decrease in SBP was revealed in HT patients who were homozygous for the 460Trp-allele than in heterozygous or homozygous individuals for the Gly460-allele (-25±4 mmHg vs. -12±2 mmHg and -14±1 mmHg, respectively, *P<0.05*). This peculiarity might be caused by environmental conditions. In our study, the antihypertensive efficacy of indapamide was equally high for Gly-allele carriers and Trp-allele carriers. However, a tendency towards a better antihypertensive response with achievement of target levels of SBP and DBP was revealed in patients with Trp-allele of the ADD1 Gly460Trp polymorphism, which is in agreement with other studies. In addition, many patients, carriers of the Trp/Trp- genotype, were classified as carriers of a "low-renin" form of HT (66.7 %) compared with other patients (23.8%) [29,30]. In contrast to the well-designed study on the ADD1 Gly460Trp polymorphism, some other studies in other populations have shown insufficient results to confirm the same correlation between ADD1 polymorphism and sodium sensitivity [29,31] or a response to diuretic therapy [32], which causes great interest in continuing the investigations. A multiple choice of antihypertensive drugs is widely available. However, a high individual variability to the antihypertensive therapy is still responsible for only a modest reduction of the CV risk and unsatisfactory control of BP levels. The success of future hypertension treatment will depend upon understanding the genetic molecular mechanisms operating in subsets of patients, and the ability of new drugs to purposefully correct such alterations. For example, the study [33] of three genes (ADD1, NEDD4L, and WNK1) related to renal sodium handling and blood pressure regulation showed impressive results. In particular, SBP decreased by 11.2 mmHg in patients with one mutated allele (ADD1 Trp), and by 15.2 mmHg in patients with two mutated alleles (ADD1 Trp and WNK1 GG). Carriers of three mutated alleles (ADD1 Trp, WNK1 GG, and NEDD4L G) were the diuretic "sensitive" patients: SAD decreased by 23.2 mmHg. Finally, on the other hand, a decrease in SAD was only 3.4 mmHg in patients carrying the wild type alleles (WNK1 AA, NEDD4L AA) on the background of the ADD1 Trp allele. Thus, the authors found the ADD1 Trp-allele to be permissive for the effects of variants of the other genes.

In conclusion, the results of our study showed high antihypertensive and cardioprotective efficacy of Indapamide treatment independently on carrying of the ADD1 Gly460Trp polymorphism. At the same time, we revealed certain advantages in the vasoprotective efficacy of Indapamide treatment in Uzbek hypertensive patients who are carriers of Gly-allele of the ADD1 Gly460Trp polymorphism.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

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Pregnancy Outcomes in Pregnant Women with Subchorionic Hematoma

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Abstract

Background: The role of subchorionic hematoma (SCH) in the first trimester of pregnancy remains open for discussion. Some authors claim that SCH does not affect the pregnancy; others have found that it is a serious risk factor for adverse pregnancy outcome. The objective of the present study was to explore the outcomes of pregnancy in patients with SCH diagnosed in the first trimester.

Methods and Results: The study involved 194 pregnant women who were in terms of 6 to 12 weeks: 115 women with SCH (Group 1) and 79 apparently healthy pregnant women (Group 2). A missed miscarriage was observed in 27/23% women of Group 1 and in 4/5% of Group 2 ($P<0.001$), recurrent threat of miscarriage in 27/23% and in 4/5% ($P<0.001$), recurrent bleeding in 14/12% and 2/3% ($P<0.02$), and the short cervix syndrome in 22/19% and 5/6% ($P<0.03$) women, respectively.

***Conclusion*:** The results of our study show that the presence of SCH adversely affects the first half of pregnancy, leading to recurrent threatened abortion, recurrent threat of miscarriage, missed miscarriage until 12 weeks of gestation, and the short cervix syndrome. **(Int I Biomed. 2015;5(3):137-140.)**

Keywords: *subchorionic hematoma; miscarriage; short cervix syndrome.*

Introduction

Vaginal bleeding during the first half of pregnancy occurs in approximately 25% of women and is associated with early pregnancy loss [1,2]. Subchorionic hematoma (SCH), intrauterine hematoma, or retrochorial hematoma are common ultrasonographic findings that may be associated with first-trimester bleeding [3]. According to the literature, the incidence of SCH in the first trimester in a general obstetric population is 3.1% [4], the frequency of SCH in the group with threatened spontaneous miscarriages is 5.2% [1], and the frequency of SCH is significantly higher in the in vitro fertilization group (22.4%) [5]. Additionally, pregnant women with SCH in the first trimester show changes in vaginal flora in the second trimester, which suggests a possible association with subchorionic hematoma and vaginal flora change [6].

Ultrasonographically detected SCH increases the risk of miscarriage in patients with vaginal bleeding and of threatened abortion during the first 20 weeks of gestation [7]. A very large first-trimester hematoma is associated with a 46% risk of adverse pregnancy outcome (spontaneous abortion and premature rupture of membranes) [3]. In the case of prolongation of pregnancy, patients with SCH have a higher risk of maternal and neonatal complications of hypertension in pregnancy, preeclampsia, placental abruption, fetal growth retardation, fetal distress, and others [4,8-10], but still there is no consensus regarding the nature of these complications. Thus, conflicting versions around SCH and its role in the gestational process leave the questions open for discussion.

The objective of the present study was to explore the outcomes of pregnancy in patients with SCH diagnosed in the first trimester.

Materials and Methods

The study was conducted in Rostov-on-Don State Perinatal Center for the period from January 1, 2013, to January 1, 2015. The study was conducted in accordance

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with ethical principles of the Declaration of Helsinki. It was approved by Rostov-on-Don State Perinatal Center Ethics Committee. Written informed consent was obtained from all participants.

The criteria for inclusion in the study were the presence of SCH diagnosed by ultrasound during 6–12 weeks of pregnancy and the presence of a viable embryo in the primary ultrasound examination. Exclusion criteria were pregnancy after assisted reproductive technologies, multiple pregnancies, and cases of detected congenital anomalies.

Ultrasound examination was performed on the PhilipsHD 11, and evaluated the coccyx-rump length, heart rate, yolk sac and its average internal diameter, localization of chorion and its structure, structural features of the uterus wall and ovary. The size, the volume of SCH, and its location and stage of development were evaluated.

A heart rate of the embryo less than 110 beats per minute was assessed as bradycardia and more than 180 beats per minute as tachycardia.

The following topographies of hematomas were determined: the bottom of the uterus, the back wall, the front wall of the uterus, the area that covers the internal os of the cervix. Localization of SCH was classified as corporal (located along the wall of the uterus, in the bottom) and supracervical (above the internal os of cervix). The size of the hematoma was determined by measuring the transverse, anterior-posterior, longitudinal dimensions with automatic calculation of volume. We classified the stages of SCH development as (1) organized, (2) with signs of organization, and (3) unorganized.

Moreover, we analyzed the following complications of pregnancy: missed miscarriage, hypertension during pregnancy, and preeclampsia; and the following complications of delivery: hypotonic bleeding, rate of placenta previa and placenta increta, premature detachment of placenta, pathology of placenta discharge, preterm delivery, premature rupture of membranes, and fetal growth retardation.

Statistical analysis was performed using StatSoft Statistica v6.0. Group comparisons with respect to categorical variables are performed using chi-square tests or, alternatively, Fisher's exact test when expected cell counts were less than 5. The probability of an adverse outcome of pregnancy was determined using logistic regression (with calculation of odds ratios (OR), relative risk (RR), and confidence intervals (CI)). A probability value of $P<0.05$ was considered statistically significant.

Results

The study included 194 pregnant women at 6 to 12 weeks of pregnancy. The study group included 115 women with SCH (Group 1); the control group (Group 2) included 79 apparently healthy pregnant women without SCH. The average age was 29.7±4.3 years in Group 1 and 29.4±5.4 years in Group 2; the groups were matched by age. The somatic status of patients in Groups 1 and 2 was identical: chronic pyelonephritis, chronic gastritis, chronic pancreatitis, and hypertension were marked in an equal percentage of cases.

Corporal localization of the hematoma was more common than supracervical – 82/71% and 33/29%, respectively. SCH volume in patients of Group 1 was 0.027 to 3.68 cm^3, median (Me) – 0.605 cm^3, interquartile range (25th and 75th percentiles) from 0.225 to 1.254 cm^3. Time of SCH formation was evaluated by echographic signs of hematoma organization: unorganized hematomas were observed in 44/38% of the women, signs of hematoma organization in 24/21%, and organized hematoma in 47/41%.

The results of our study show that the presence of SCH adversely affects the first half of pregnancy. The incidence of adverse pregnancy outcome in the first trimester in pregnant women of Group 1 was significantly higher compared with Group 2. Missed miscarriage was observed in 27/23% women of Group 1 and in 4/5% of Group 2 ($P<0.05$). In addition, a higher frequency of recurrent threat of miscarriage, recurrent bleeding, and the short cervix syndrome were observed in women of Group 1. At the same time, the presence of SCH increased the chance of the first half of pregnancy complications (recurrent threatened abortion, short cervix syndrome, recurrent vaginal bleeding in pregnancy) and adverse pregnancy outcomes in the first trimester (Table 1). The risk of pregnancy loss during the terms of 6 to 12 weeks in Group 1 patients was 4.64 times higher than those in Group 2 ($P=0.0005$). Missed miscarriage during terms of 13 to 22 weeks was observed in 3/2.6% patients of Group 1 and was not observed in Group 2.

Table 1.

Complications of the first half of pregnancy in patients with SCH and in the control group

Complications of the first half of pregnancy	Group 1 (n=115)	Group 2 (n= 79)	Yates' chi-square *P-value*	RR, 95% CI, and *P-value*	OR, 95% CI, and *P-value*	Logistic regression *P-value*
Missed miscarriage (6-12 weeks)	27 (23%)	4 (5%)	10.496 *P<0.0012*	4.64 (1.69-12.73) *P=0.0029*	5.75 (1.93-17.18) *P=0.0017*	*0.0005*
Missed miscarriage (13-22 weeks)	3 (3 %)	0 (0%)	-	-	-	-
Recurrent threatened abortion	27 (23%)	4 (5%)	10.496 *P<0.0012*	4.64 (1.69-12.73) *P=0.0029*	5.75 (1.93-17.18) *P=0.0017*	*0.0005*
Short cervix syndrome	22 (19%)	5 (6%)	5.382 *P<0.0203*	3.02(1.20-7.64) *P=0.0195*	3.5 (1.26- 9.69) *P=0.0158*	*0.0115*
Recurrent vaginal bleeding	14 (12%)	2 (3%)	4.55 *P<0.0329*	4.81 (1.12-20.58 *P=0.0342*	5.34 (1.18-24.18) *P=0.0298*	*0.0168*

Table 2.

Complications of the second half of pregnancy and delivery in patients with SCH and in the control group

Complications of the third trimester	Group 1a (n=85)	Group 2a (n= 63)	Fisher's exact test (2-Tail) *P-value*	RR, 95% CI, and P-value	OR, 95% CI, and *P-value*	Logistic regression *P-value*
Hypertension associated with pregnancy	1 (1.2%)	1 (1.6%)	*1.0*	0.74 (0.05-11.62) *P=0.8311*	0.74 (0.04-12.03) *P=0.8311*	*>0.05*
Preeclamsia	3 (3.5%)	1 (1.6%)	*0.6367*	2.22 (0.24-20.88) *P=0.4844*	2.27 (0.23- 22.34) *P=0.4838*	*>0.05*
Hypotonic bleeding	1 (1,2%)	0 (0%)	*1.0*	-	-	-
Placenta previa	3 (3.5%)	1 (1.6%)	*0.6367*	2.22 (0.24-20.88) *P=0.4844*	2.27 (0.23- 22.34) *P=0.4838*	*>0.05*
Placenta increta	1 (1.2%)	0 (0%)	*1.0*	-	-	-
Placental abruption	2 (2.3%)	0 (0%)	*0.5077*	-	-	-
Retained portions of placenta	0 (0%)	2 (3.2%)	*0.1795*	-	-	-
Preterm birth	8 (9.4%)	1 (1.6%)	*0.07878*	5,93 (0.76- 46.21) *P=0.0893*	6.44 (0.78- 52.90) *P=0.0829*	*>0.05*
Preterm rupture of membranes	2 (2.3%)	0 (0%)	*0.5077*	-	-	-
Intrauterine growth retardation	8 (9.4%)	9 (14.3%)	*0.4371*	0.66 (0.27- 1.61) *P=0.3607*	0.62 (0.23-1.72) *P=0.3609*	*>0.05*

Women with prolonged pregnancy (85/74%) were subjected to further clinical monitoring (Group 1a), including the analysis of long-term complications of pregnancy and its outcomes. The control group of patients with prolonged pregnancy (Group 2a) included 63 apparently healthy women out of 79 women participating in the evaluation in the first trimester, 12 of which ended in surgical abortions on request up to 12 weeks, and 4 of which ended in missed miscarriage up to 12 weeks.

Statistical processing using logistic regression showed how many times the chances of complications increase during the second half of pregnancy in the presence of SCH in the first trimester (Table 2). Analysis of perinatal outcomes in patients with SCH in our study showed that in this group of pregnant women the risk of preterm birth, preeclampsia, hypertension associated with pregnancy, premature rupture of membranes, placenta previa, placenta increta, placental abruption, retained portions of placenta, and fetal growth retardation is not different from pregnant women without SCH.

However, the rate of preterm birth in Group 1a was significantly higher than in Group 2a: 9.4% vs. 1.6% *(P<0.05*); that definitely needs a further study, with the expansion of sample size and analysis of received data.

Discussion

The results of our study show that the presence of SCH adversely affects the first half of the pregnancy. The incidence of pathological placentation, recurrent threatened abortion, recurrent threat of miscarriage, and missed miscarriage was higher in pregnant women with SCH. Our results relating the correlation between SCH and missed miscarriage are consistent with those published in other studies [4,9]. S. Nagy et al. [4] found that 18.7% of women had subsequent pregnancy loss in terms less than 24 weeks.

M. Tuuli et al. [9] found that patients with SCH had 2.18 higher risk of spontaneous abortion. In addition, the results of our study show that patients with SCH have higher frequency of short cervix syndrome.

In a univariable analysis [10], the presence of a SCH was significantly associated with a shorter mean cervical length as well as a cervical length less than the 10th percentile (4.27 cm vs 4.36 cm, *P=0.038*; 1.9% vs 0.5%, *P=0.006*, respectively); preterm birth also was more common in women with an SCH (12.5% vs 7.3% in women without a first-trimester SCH, *P=0.001*). The fact that first-trimester SCH is associated with both a shorter cervical length and preterm birth suggests the possibility that mechanisms other than cervical shortening may be involved in preterm birth pathogenesis.

We did not find a correlation between the presence of SCH diagnosed at 6 to 12 weeks and late pregnancy complications: preeclampsia, hypertension associated with pregnancy, preterm labor, premature rupture of membranes, placenta previa, placenta increta, placental abruption, retained portions of placenta, and fetal growth retardation.

In the discussion of the results, it should be said that even among those who find a correlation between SCH and late complications of pregnancy, there is no unanimity of opinion on the nature of these complications. Thus, S. Nagy et al. [4] found that patients with SCH had higher risk of preeclampsia, placental abruption, preterm delivery, fetal growth retardation, and higher frequency of children born

with less weight than in women of the control group [4]. S. Norman et al. [8] published the results of a retrospective study and partly confirmed the results of S. Nagy et al. [4], showing a link between subchorionic hematoma and placental abruption, subchorionic hematoma and preterm delivery, but did not find a correlation between SCH and other complications of the gestational process: premature rupture of membranes, fetal growth retardation, fetal death and preeclampsia. Later, in 2011, M. G. Tuuli et al. [9] published a meta-analysis of studies of perinatal outcomes in patients with SCH which showed that patients with SCH had a 2.18 higher risk of spontaneous abortion, 2.9 higher risk of stillbirth, 5.7 higher risk of placental abruption, 1.4 higher risk of premature births and 1.64 higher risk of premature rupture of membranes. This analysis did not find a correlation between SCH and preeclampsia, hypertension associated with pregnancy, and low birth weight.

We should especially mention the frequency of preterm birth in pregnant women with SCH. In our study, we found a high incidence of preterm birth in women with SCH; however, we did not find significant differences between patients with and without SCH. In several large studies such an association was found [4,8-10]; however, those studies included large samples of pregnant women, and some have used other inclusion criteria. For example, S. M. Norman et al. [8], showed that women with ultrasound-detected SCH before 22 weeks of gestation are at increased risk of preterm delivery.

A large number of studies on the clinical value of SCH in the genesis of pregnancy complications underline the relevance of the considered clinical problem, and the role of SCH in the genesis of obstetric complications. Contradictions in the published results may be partly due to both objective and subjective reasons, such as ethnographic characteristics of the population, different inclusion criteria, and different terms of pregnancy of patients included in the study.

In summary, the results of our study show that the presence of SCH adversely affects the first half of pregnancy, leading to recurrent threatened abortion, recurrent threat of miscarriage, missed miscarriage until 12 weeks of gestation, and the short cervix syndrome.

Competing interests

The authors declare that they have no competing interests.

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Characterizations of Bacterial Vaginosis among HIV-positive and HIV-negative Pregnant Women

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Abstract

***Objective**:* The aim of this study was to find the characteristics of bacterial vaginosis (BV) among HIV-infected and HIV-negative pregnant women at ABUTH, Zaria.

Study design: Case control and laboratory-based design, conducted from August 2, 2011, to December 30, 2011. BV was defined using Amsel's criteria, which uses 3 out of 4 diagnostic criteria to diagnose BV.

Results: Two hundred HIV-positive and 200-HIV negative women were included in the study. The mean age was 26.3 years with a range from 17 to 41 years. The prevalence rate of BV irrespective of HIV status was 33.2%. In HIV-positive pregnant women, the prevalence was 46.0%; in HIV-negative pregnant women, the prevalence was 20.5% (OR=3.30; 95% CI: 2.1-5.1, *P<0.05*). Hence, HIV-positive pregnant women were significantly more likely to have BV. BV was most prevalent in the age group of 30 to 34 years, with 49% positive, and in those with parity between 1 and 4, with a prevalence of 41.5%. It is least common in primigravidae with 19%. Prevalence among HIV-positive pregnant women whose CD4 > 350cells/mm^3 was 22%, and for those whose CD4 was < 350 cells/mm^3 prevalence was 67% (OR=7.05; 95% CI: 3.7-13.3, *P<0.05*).

Conclusion: BV is more prevalent among HIV-positive pregnant women than their HIV-negative counterparts, and its occurrence is higher among those with the lower CD4 count; therefore, reducing the prevalence of HIV among pregnant women and improving the CD4 count among HIV-positive pregnant women would reduce the prevalence of BV and its consequences. **(Int J Biomed. 2015;5(3):141-146.)**

Keywords: *Bacterial Vaginosis; HIV transmission; Amsel's criteria.*

Introduction

BV is a common vaginal infection that involves the disruption of the balance of bacterial flora in the vagina with the overgrowth of specific bacteria. Normally, bacteria belonging to the *Lactobacillus* type live in the vagina as commensals. In BV, however, increased numbers of bacteria, such as *Gardnerella vaginalis, Bacteroides spp, Mobiluncus spp, Prevotella spp* and *Mycoplasma hominis,* replace them [1]. The reported prevalence of BV in pregnant women ranges from 14% to 21% in Western countries [2-4], and a prevalence rate of 40.8% was reported in a non-pregnant population in southern Nigeria [5]. A case study done in Ghana showed a low prevalence of 1.4% among antenatal women [4]. An estimated 25% to 30% of women have BV at any time, mostly without signs such as fishy odor or discharge [1,4], and this rises to 85% in prostitute populations [2,3].

A study of pregnant women demonstrated that women who had BV on screening were 5 times more likely to have preterm labor or late miscarriage than those without the condition [5]. In women delivered by Caesarean section, those with BV were nearly 6 times more likely to develop postpartum endometritis than those without BV despite antibiotic prophylaxis, and BV was the strongest predictor of postpartum endometritis irrespective of mode of delivery [6]. Of greater clinical importance is the link between BV and HIV infection. Apart from its association with adverse pregnancy outcomes, BV is associated with increased risk of sexual acquisition of HIV [1,3,8]. There is evidence to support several mechanisms through which BV and other reproductive tract infections facilitate HIV transmission [7]. Genital tract

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infection with *G. vaginalis,* which is commonly isolated in BV, has been shown to be able to stimulate HIV-1 reproduction and hence increase the likelihood of sexual transmission [8]. Measurement of HIV in genital secretions indicates that HIV infectiousness and susceptibility may be greater in the presence of concurrent reproductive tract infections [8,9]. Also significant is the sharp decline in the concentration of HIV in genital secretions when the infection is treated [1,2,8].

Several cross-sectional studies performed in Thailand, Uganda, and Malawi, showed that BV women had an increased incidence of HIV infection. A prospective study in Kenya also showed that the presence of BV and the absence of lactobacilli or absence of hydrogen peroxide-producing lactobacilli upon examination, were all significantly associated with acquisition of HIV infection at follow-up [1,2]. Studies of the impact of BV on HIV infections showed varying degrees of increased risk of infection [2]. Some investigators calculate that in a population where the baseline risk of seroconversion is 2%, one additional case of HIV infection would occur for every 80 to 90 cases of vaginosis. "These data suggest that greater attention needs to be given to bacterial vaginosis in the global fight against HIV infection" [1].

In view of the relationship between BV and HIV infection and also the associated risk of adverse obstetric sequelae, including increased vertical transmission of HIV during pregnancy, screening women for BV and treating those infected is a major strategy in the primary and secondary prevention of HIV as well as reducing risk of mother-to-child transmission of HIV, particularly in settings of high HIV seroprevalence.

The aim and objectives

The aim of this study was to find the characteristics of BV among HIV-infected and HIV-negative pregnant women at ABUTH, Zaria.

The specific objectives are to:

- Determine the prevalence of BV among HIV-infected pregnant women
- Determine the prevalence of BV among HIV-negative pregnant women
- Compare the prevalence of BV in the two groups
- Ascertain any relationship between the presence of BV and the immunological status of HIV-infected pregnant women
- Derive recommendations relevant to BV that will benefit the study population, and could be scaled up

Null Hypothesis: There is no statistically significant difference in the prevalence of BV between pregnant women who are HIV-positive and those who are HIV-negative in the same clinical setting.

Materials and Methods

Study area and design

The study was case controlled in design and involved both clinical and laboratory- based components. The clinical segment of the study was carried out simultaneously at the PMTCT and antenatal clinics of ABUTH, while the laboratory analyses were made at the AIDS Prevention Initiative in Nigeria (APIN)/Harvard/PEPFAR supported laboratory of ABUTH, Zaria..

The study participants were selected from the antenatal clinic after obtaining informed written consent for participation in the study.

The sample size for the study was determined using the formula below, and BV prevalence among HIV-negative pregnant women of 14% [1-4].

$$N = \frac{Z^2 pq}{D2}$$, where

N- Minimum sample size
Z- 1.96 at 95% confidence level
P - Prevalence of the condition
D- Level of significance, 0.05 at 95% confidence level

This gave a minimum sample size of 185 for each group. A 10% attrition rate was 18.5; this was approximated to 15, giving a total of 200 for HIV-positive pregnant women and 200 for HIV-negative pregnant women as controls for the study.

For every HIV-infected patient recruited at the PMTCT clinic, an HIV-uninfected patient of similar age, parity, and socioeconomic status was recruited as control from the ANC until the total number of 200 was obtained in both groups (Table 1 and 2). Using convenience sampling technique, we selected consecutive pregnant women who consented and met the inclusion criteria.

Table 1.

Age and parity of both groups' patients

	Parity of HIV-positive pregnant women			Parity of HIV-negative pregnant women			
Age group	0	1-4	≥5	0	1-4	≥5	Total
15-19	3	4	-	3	4	-	14
20-24	14	30	-	14	30	-	88
25-29	12	44	2	12	44	2	116
30-34	8	31	10	8	31	10	98
35-39	4	14	15	4	14	15	66
≥40	-	6	3	-	6	3	18
Total	41	129	30	41	129	30	400

Those diagnosed with BV were treated free-of-charge using tabs Metronidazole 400 mg, 8 hourly, for 7 days.

The following criteria were used to select the participants for the study:

- Informed consent to participate in the study
- Those women who had gone through HIV pre-test counseling and testing (HCT) by ABUTH PMTCT

nurse counselors

- Those who were reported as HIV-positive after undergoing the double rapid serial testing according to the National HIV Testing Algorithm and received post-test counseling
- Pregnant women who were reported as HIV-negative by double rapid serial testing and received post-test counseling were recruited as controls (matched for age and parity).
- The diagnosis of BV was based on the Amsel diagnostic criteria (Table 3) [9].

Table 2.

Socio-demographic data of patients

Variable	HIV- positive		HIV-negative		Total
	n	%	n	%	
Marital Status					
Married	198	49.7	200	50.3	398
Single	-	-	-	-	
Divorced	-	-	-	-	
Widowed	2	100	0	0	2
Highest Educational Attainment					
Primary	22	68.8	10	31.2	32
Secondary	70	53.0	62	47.0	132
Tertiary	74	40.0	111	60.0	181
Quranic	28	62.2	17	37.8	45
None	6		4		10
Marriage Order					
First	122	39.1	190	60.9	312
Second	74	91.3	7	8.4	81
Third	4	57.1	3	42.8	7
Marriage Type					
Monogamy	140	47	158	53.0	298
Polygamy	60	58.8	42	41.2	102
Total Number of Partner over time					
1-2	100	50.2	99	49.8	199
3 or more	76	51.7	71	48.3	147
Missing:54(13.5%)					

Table 3.

The Diagnosis of BV based on the Amsel diagnostic criteria

Laboratory findings	HIV-positive		HIV-negative	
	positive n (%)	negative n (%)	positive n (%)	negative n (%)
Whiff test	108 (27%)	88 (22%)	102(25.%)	80(20%)
PH (> 4.5)	102(26%)	100(25%)	132 (33%)	76 (19%)
Clue cells	125(31.2%)	92 (23%)	58(14.5%)	73(18.2%)
V. discharge	106(26.5%)	142(35.5%)	56 (14%)	137(34.2%)

Approval for the study was obtained from the ABUTH Ethical Review Committee. Doctor and nurse interviewers who were specifically trained for the study screened each woman for eligibility, explained the purpose and practice of the study and obtained informed written consent, which was written in English and translated for those who could not read English.

The instrument used was a pre-tested, semi-structured proforma. It was used to collect socio-demographic information, medical history, HIV infection characteristics, clinical "bedside" test results, and BV laboratory findings. Trained nurses and the author administered the questionnaire. The clinical "bedside" test was done by the author, and other information, such as CD4 count, was obtained from the patients' records. The laboratory scientist filled in the laboratory (clue cells) findings

The data assembled on the questionnaires were cleaned. A database was developed using SPSS 16.0 version for Windows and data entry was made into it. Further data cleaning was done before analysis was commenced, and relevant tables and graphs were generated where appropriate. The chi-square test was used to determine the strength of association between exposure and outcome variables in the experimental and controlled groups. A probability value of $P<0.05$ was considered statistically significant.

Specimen materials for making laboratory diagnosis were collected during a comprehensive pelvic examination. Following adequate counselling, each subject was placed in the dorsal position on an examination couch in the clinic. Using a sterile disposable Cusco speculum to expose the cervix and posterior fornix, the clinician evaluated the nature of the discharge, and a specimen from the posterior fornix was taken with a sterile swab stick. The classical BV discharge is characterized by a thin, homogeneous discharge, grey/ yellow in colour. However, absence of the classical discharge did not rule out disturbed vaginal flora. Two basic methods of diagnostic testing were used: laboratory-based and clinical 'bedside' testing. For the purposes of laboratory-based testing, the swab was taken from the posterior vaginal fornix, diluted with normal saline and allowed to air dry, then kept in a slide rack which was used to transport the slides to the laboratory where they were gram stained and examined under the microscope (X400).

Diagnosis of BV by Amsel Criteria (Amsel et a.l, 1983)

The pH of the vagina was determined directly with the use of Combi 9 pH sticks placed on the posterior-vaginal fornix, after exposing the cervix with a sterile Cusco speculum that was inserted into the subject placed in the dorsal position. A swab stick was used to obtain a specimen which was then extracted into 0.2 mL of physiological saline on a glass slide. A drop of 10% potassium hydroxide was placed on another glass slide. The swab was then stirred in the 10% potassium hydroxide and immediately evaluated for the presence of a fishy odor. The extracted drop was placed in a slide rack and allowed to air dry. The slides were transported to the laboratory for examination, for detection of clue cells by Gram stain microscopy, which was examined under X100 objective for clue cells, at ART laboratory of the Ahmadu Bello University Teaching Hospital, Zaria.

Limitation of the study: a) The fact that Amsel's criteria used 3 of 4 diagnostic criteria made diagnosis very cumbersomeb) The unavailability of a single diagnostic test made the study unduly expensive; c) Matching of the patient for age parity was difficult; We had to obtain the sample on different days.

Results

1. The 200 HIV-negative pregnant women that were ultimately recruited as controls in this study were secured from 239 eligible women: 15 were dropped during the process of matching for age and parity of the study group; 15 failed to return/complete the consent forms, and another 9 were replaced after their specimens encountered a number of mix-ups in the laboratory. To secure the 200 sample size of HIV-positive pregnant women, a total of 209 eligible women were recruited, with the following attrition: 3 women failed to return/complete the consent forms, 4 had wrong numbering of specimens in the laboratory, and 2 incurred broken slides, also in the laboratory.

This study was conducted between August 2 and December 30, 2011, during which period a total of 757 new antenatal attendees were seen in the facility where the study was carried out. Out of these 98 were HIV-positive, 7 of whom were newly diagnosed with HIV. This gave a clinical HIV prevalence of 12.9% during the study period. The overall prevalence rate of BV in this study irrespective of HIV status was 33.2%.

2. Prevalence of BV among HIV-positive pregnant women was 46.0% (Table 4).

Table 4.

Prevalence of BV and HIV status of pregnant women at ABUTH Zaria

HIV status	BV				
	positive n (%)	negative n (%)	*P*	OR	95% CI
HIV-negative	41(20.5%)	159(79.5%)		1.0	
HIV-positive	92(46.0)	108(54.0%)	*0.000*	3.30	2.1-5.1
Total	133(33.2%)	267(66.8%)			

In this HIV group, BV was more commonly associated with tribe, religion, and parity, with *P*-values of 0.001, 0.03 and 0.04, respectively, which were all statistically significant. Other factors that did not show any statistical significance were level of educational attainment, order of marriage, type of marriage, number of partners over time, age of the subject, occupation, and gestational age, with *P*-values of 0.07, 0.62, 0.36, 0.22, 0.06, 0.28 and 0.055, respectively, as their *P-values* were *>0.05.*

3. BV prevalence among pregnant women who were HIV-negative was 20.5%

In those who were HIV-negative, BV appeared to be more commonly associated with level of educational attainment and the age of the subject, with *P*-values of 0.024 and 0.025, respectively, which were both statistically significant. Other factors that did not show any statistical significance were order of marriage, type of marriage, number of partners over time, tribe, religion occupation, gestational age, and parity, with *P*-values of 0.25, 0.28, 0.31, 0.29, 0.40, 0.34, 0.49 and 0.29, respectively, as their *P-values* were *>0.05.*

4. The odds of occurrence of BV in HIV-infected women was 3 times higher than among HIV-uninfected women (OR=3.30; 95% CI: 2.1-5.1, *P<0.05*).

5. The pattern of BV prevalence among those who were HIV-positive at various levels of CD4 count were as follows: For those with CD4 > 350 cells/mm^3 the prevalence rate was 22%, and for those with CD4 < 350 cells/mm^3 the rate was 67%. The odds of BV occurrence in HIV-infected women with CD4 count of ≤ 350 cells/mm^3 was 7 times higher than in HIV-infected women whose CD4 count was > 350 cells/mm^3, and this was statistically significant (OR=7.05; 95% CI: 3.7-13.3, *P<0.05*) (Table 5).

Table 5.

The pattern of BV among HIV- positive pregnant women and their CD4 count

CD4 cells/mm^3	BV				
	positive	negative	*P*	OR	95% CI
≤ 350	71(67.0%)	35(33.0%)		1.00	
> 350	21(22.3%)	73(77.7%)	*0.000*	7.05	3.7-13.3
Total	92(46.0%)	108(54.0%)			

Discussion

This case-control study was done to determine the prevalence of BV among HIV-positive antenatal women, compared to their HIV-negative counterparts, and to relate the presence of BV to their immunological status at ABUTH, Zaria.

The prevalence of BV in both case and control group was found to be 33.2%. The prevalence of BV among HIV-infected pregnant women in this study was 46% compared to 20.5% among HIV-uninfected women. This difference is statistically significant (OR=3.30, *P=0.000*), thus suggesting that HIV is a significant exposure risk for BV. Therefore, some HIV clinics also provide sexual health screens and test for BV as part of their care [10].

Demographically, in the HIV-positive pregnant group, BV was more commonly associated with tribe, religion, and parity. Tribe and religion may be associated with socio-cultural habits, including risk practices that may include douching with vaginal washes or soaps; other things inserted in the vagina erroneously include tampons, pads, powders and sprays. The use or non-use of contraceptives and the type might affect the prevalence of BV: hormonal contraceptives are protective of BV [8,11] while intrauterine contraceptive devices have been associated with increased susceptibly to BV [10,12]. These are all dependent on tribal and religious beliefs [12]. The prevalence of BV was highest among multiparous (1–4) women (54%) compared to nulliparous women, and this was statistically significant. This could be due to the fact that multiparous women are more likely to have had more sexual intercourse, which is a known risk factor, and also because of the drop in cellular immunity in this group of patients [8,13]. Parity was not a significant factor among the HIV-negative group.

Demographically, in the HIV-negative group, BV was

more commonly associated with the level of educational attainment and the age of subject. It was higher among those with no form of education. Low education has been linked to higher BV-risk in the literature [14]. It was more prevalent in the age group 30–34 years (37.8%), which was significant. This could be due to the fact that this age group is in the active reproductive period and patients are more sexually active. Other studies showed a high prevalence in the age group 25 to 29 years [14,15].

Demographically, in both groups, BV was more prevalent in the second trimester though this was not statistically significant. This could be as a result of late booking: mean gestational age at booking was 20 weeks. All the women studied were married except two that were widowed. Though the prevalence of BV was equal among women in monogamous and polygamous unions, women who were BV-negative were more likely to be in monogamous marriages than in polygamous marriages. This could be explained by the fact that those in monogamous settings are less likely to have multiple sexual partners than their polygamous counterparts. Having multiple sexual partners has been identified as a risk factor [10,16,17], although the number of partners over time was not significantly associated with BV. Many (13.5%) were too shy to give information on their number of partners, considering its sensitive nature, especially in northern Nigeria were this study was conducted.

In HIV-positive pregnant women, considering one of the criteria for instituting HAART (CD4 count), among those with CD4 count $\leq$ 350 cells/mm^3, the prevalence of clinical BV was 67%. This was 7 times higher than in those who had CD4 counts greater than 350 cells/mm^3, in whom the prevalence rate was 22.3% and was similar to the prevalence rate of 20.5% among HIV-uninfected pregnant women. It is possible that HIV infection alters the local immune mechanism in the lower genital tract, which puts those women with HIV at higher risks for the BV organism to thrive and proliferate in the vagina [8,17]. Furthermore, studies have shown that HIV load in the genital tract correlates positively with BV and inversely with the absence of BV [1,12,17]. The increase in HIV load in the genital tract of BV women leads to more exposure to this high viral load during the process of labor and delivery, thereby increasing the risk of mother-to-child transmission of HIV if this infection is not identified and treated in pregnancy [1,2]. These results, therefore, imply that identification and treatment of BV is an important strategy in the prevention of HIV transmission, particularly with respect to mother-to-child transmission.

Cell-mediated immunity is an important component of protection against genital tract pathogens; the higher the number of memory T-cells the better protection against infections [2]. T-cells are the main target of HIV in the blood, and they act as the host the virus needs to replicate. One important feature of the T-cell's structure is the CD4 receptor site; once these "coordinator" T-cells are hijacked, the immune system is annihilated, leaving the body open to infections [2,17]. Therefore, the CD4 count is a good reflector of the immune system; hence the lower the CD4 count, the higher the prevalence of BV, as shown in this study.

To detect clue cells, the gram stained smear has been found to have higher sensitivity and specificity [11,12,15]. Despite this, none of the 4 criteria was as accurate as it should have been, hence the need for the composite criteria [14,18,19]. It is also possible that not all BV patients had the offending organisms diagnosed. This may be due to the use of antibiotics or antiseptic soaps or preparations for douching prior to presentation at the clinic [14,19].

Conclusion

This is probably the first case control study in Nigeria that compared the prevalence of BV among pregnant women who are HIV-positive and their HIV-negative counterparts and that related the presence of BV to the immunological status of the HIV-positive antenatal group. The prevalence of BV infection among HIV-infected pregnant women is 3 times higher than among their HIV-negative counterparts. Likewise, the prevalence of BV is 7 times higher among HIV-infected pregnant women whose CD4 counts were < 350 cells/m^3 compared to those whose CD4 were >350 cells/mm^3 in ABUTH, Zaria.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

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Diagnostic Value of the Visual Evoked Potential Investigation in Optic Neuritis

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Abstract

Objective: Comparative analysis of the results of the visual evoked potential investigation according to stages of optic neuritis (ON).

Material and Methods: The study included 90 patients (90 eyes) with different stages of ON. A control group comprised 10 somatically healthy persons (10 eyes) of the same age without ophthalmic pathology. All examined underwent standard ophthalmologic examination, including visometry, tonometry, perimetry, and ophthalmoscopy, as well as optical coherence tomography (OCT) and visual evoked potentials (VEP) determination.

Results: The VEP parameters provide identification of the functional disorders of the optic nerve. Our results showed that there is delayed latency and reduced amplitude of the P100 component in patients with ischemic and atrophic stages of the disease. In ON, P100 was the most informative index. We noted that the N145 parameter in ON is not very informative.

Conclusion: An estimation of VEP parameters provides a more reliable diagnosis of the stage of disease and aids in monitoring the effectiveness of treatment. **(Int J Biomed. 2015;5(3):147-150.)**

Keywords: *optic neuritis; visual evoked potentials (VEPs); optical coherence tomography (OCT).*

Introduction

Many clinicians emphasize the importance of the study of visual evoked potentials (VEPs) to evaluate visual pathway function and obtain information on the functional status of the axons and myelin sheath of the optic nerve [1-3]. VEPs represent the visual pathway from the retina along the optic nerve, optic chiasma, optic tract, and optic radiation to the occipital optical cortex [4-7].

VEPs registration is a valuable diagnostic test in the evaluation of patients with ON. Verification of the visual pathway lesion is particularly important in the absence of changes in the fundus in patients with retrobulbar neuritis and early stages of inflammation of the optic nerve [8-14]. Despite the large number of articles devoted to this issue, the dynamics of changes in VEPs in ON are still under discussion.

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Objective: Comparative analysis of the results of the visual evoked potential investigation according to stages of optic neuritis (ON).

Material and Methods

The study included 90 patients (90 eyes) with different stages of ON of an inflammatory etiology. A control group comprised 10 somatically healthy persons (10 eyes) of the same age without ophthalmic pathology. Exclusion criteria included conjunctivitis, uveitis, glaucoma, ON of a demyelinating etiology, as well as the degenerative, ischemic, vascular and oncological diseases of the eye.

All examined underwent standard ophthalmologic examination, including visometry, tonometry, perimetry, and ophthalmoscopy, as well as optical coherence tomography (OCT) and VEP determination. VEPs were performed with a Neuron-Spectrum-4 EPM apparatus by presenting an alternating chessboard pattern and single light pulses.

Patients were distributed in groups according to the classification of ON, depending on the condition of the optic

disk (OD) [13]. Group 1 included 28 patients (28 eyes) with hyperemia of the OD, Group 2 included 21 patients (21 eyes) with edema of the OD, Group 3 included 26 patients (26 eyes) with ischemia of the OD, and Group 4 included 15 patients (15 eyes) with glial atrophy of the OD.

The study was conducted in accordance with ethical principles of the Declaration of Helsinki. It was approved by the Tashkent Institute of Postgraduate Medical Education Ethics Committee. Written *i*nformed consent was obtained from all participants.

Statistical analysis was performed using the statistical software Statistica for Windows 6.0. Differences of continuous variables with a normal distribution (presented as M±SEM) between the two groups were calculated using the independent-sample t-test A probability value of $P<0.05$ was considered statistically significant.

Results and Discussion

The visual acuity values were 0.62±0.05, 0.31±0.06, 0.22±0.04, and 0.03±0.01 in Groups 1, 2, 3, and 4, respectively. The anterior segment of the eyeball was unchanged in biomicroscopy.

During direct ophthalmoscopy, in Group 1 we noted hyperemia of the OD, lack of clarity in borders along the vessels, and an increase to 18.4±2.0 in the number of vessels passing through the edge of the disc; arteries had normal caliber, veins were extended, and macular reflex was saved. During OCT we observed normal levels of thickness of the retinal nerve fiber layer (RNFL) and the OD.

In Group 2, the OD was sharply hyperemic, borders were unclear, and the number of vessels passing through the edge of the disc was increased to 22.4±2.0; there was marked swelling of the OD and peripapillary zone, arteries and veins were dilated, and macular reflex was reduced. We observed an increased RNFL thickness in OCT, as well as the area of the OD.

In Group 3, the OD was pale and edematous with fuzzy borders, and the number of vessels passing through the edge of the disc was 14.2±2.0; we marked swelling of the peripapillary zone, narrowed arteries and extended veins, and a reduction in macular reflex. In OCT, RNFL thickness was significantly reduced in comparison with Group 2 ($P<0.01$) (Table 1).

In Group 4, the OD was pale, borders along the vessels were unclear, the number of vessels passing through the edge of the disc was 11.3±2.0, the arteries and veins were narrowed, and macular reflex was absent. The average RNFL thickness was significantly lower compared to the values in Groups 2 and 3 ($P<0.001$). Parameters of the rim area and the area of the OD had no significant differences in comparison with other groups (Table 1).

When VEPs checkerboard stimulus was used, peak latencies of N75 (1st channel) significantly increased in Group 1 (78.26±1.04 ms) compared with the control group (75.2±0.2 ms; $P<0.05$). The prolonged latency evidenced reduced impulse conduction along the visual pathways. There was also a statistically significant increase in the latency of N75 in Group 2 (81.64±2.09 ms) compared to control ($P<0.05$). In Group 3, this parameter increased up to 93.14±3.57 ms and was statistically greater vs. Group 2 ($P<0.01$), but a significant difference compared with Group 4 (98.22±6.38 ms) was not detected. The prolonged latency indicates the defeat of the myelin sheath, which is associated with the reduced impulse conduction along the visual pathways.

Table 1.

Comparative characteristics of the morphometric parameters of the OD

Group	Rim Area	Disc Area	RNFL	Cup Volume
Group 1	1.65±0.08	2.00±0.07	105.7±2.51	0.07±0.02
	P1>0.05 P2<0.001	*P1>0.05 P2<0.01*	*P1>0.05 P2<0.001*	*P1<0.05 P2<0.01*
Group 2	2.70±0.25	2.60±0.16	295.38±19.15	0.003±0.002
	P1<0.01 P3>0.05	*P1>0.05 P3<0.05*	*P1<0.001 P3<0.001*	*P1<0.001 P3>0.05*
Group 3	2.28±0.19	2.12±0.10	142.83±8.15	0.004±0.003
	P1<0.05 P4<0.01	*P1>0.05 P4<0.05*	*P1<0.01 P4<0.001*	*P1<0.001 P4<0.01*
Group 4	1.53±0.08	1.74±0.10	92.99±2.73	0.03±0.008
	P1>0.05	*P1>0.05*	*P1>0.05*	*P1<0.05*
Control group	1.48±0.29	2.26±0.5	104.5±6.9	0.24±0.02

P1 – vs. the control group; P2 – Group 1 vs. Group 2; P3 - Group 2 vs. Group 3; P4 - Group 3 vs. Group 4.

In assessing the form of the P100 component, the impairment of the VEP configuration in the form of P100 splitting was detected. The W-like shape of P100 peak reflected the presence of a central scotoma in the visual field or partial atrophy of the optic nerve, which was confirmed by other researchers [5,10].

Almost all the subjects showed an increase in P100 latency from 10 to 30 ms compared to the upper limit of normal values upon checkerboard pattern stimulus. In Group 1, this parameter was 109.86±2.11 ms, which was significantly higher vs. the control group ($P<0.05$). In the stages of edema and ischemia, this parameter tended to increase, and amounted to an average of 112.73±3.52 ms ($P<0.05$) and 123.65±3.93 ms ($P<0.05$), respectively. We also registered an increase in latency in Group 4 by 20% to 25%; the average value of latency was 127.24±7.34 ms ($P<0.05$) and ranged from 118 to 135 ms.

In the analysis of the N145 component in 1 and 2 channels, we did not find any significant differences between the patient groups and control. The parameters of the latency of the VEPs are shown in Table 2. Evaluation of latency of the N75 and P100 components (in 2nd channel) in patients with different stages of ON revealed a statistically significant increase in the estimated parameters ($P<0.05$).

Analysis of N75-P100 amplitude revealed a significant increase in this indicator in Groups 1 and 2 compared with the control group: 13.91±0.79 μV and 15.77±1.29 μV, respectively, and $P<0.05$ in both cases. Ischemia, toxic effects of exudates, compression of nerve fibers, and disintegration of the myelin sheath of nerve fibers occur in the acute phase of neuritis. Increasing the amplitude of the N75-P100 component apparently was connected with the reactive stimulation of

axons of the optic nerve due to exudative reactions occurring in the shell of the optic nerve. The amplitude of the N75-100 component was significantly decreased in Group 3 (6.76±0.76 μV) compared with the control group (*P<0.05*), as well as with Group 2 (*P<0.001*). The reduction of VEP amplitude is associated with the blockage of pulse conduction, probably due to the damage of the axial cylinders of axons. Reduction of amplitude indicates a decrease in the number of functioning axons. A significant reduction in the amplitude of the N75-P100 component (3.68±0.4 μV, *P<0.05*) was observed in Group 4 (patients with OD atrophy). The reduction in VEP amplitude is correlated with changes in visual functions (r=0.42), which indicates the death of nerve fibers. Changes in VEP amplitude are presented in Table 3. Analysis of the amplitude of the P100-N145 component revealed a significant increase in this indicator in Groups 1 and 2 compared with the control group: 12.73±1.06 μV and 13.31±0.94 μV, respectively, and *P<0.05* in both cases. The amplitude of the P100-N145 component was significantly decreased in Group 3 (7.54±0.83 μV) compared to Group 2 (*P<0.001*). No significant differences, compared to the control group, were detected. A significant reduction in the amplitude of the P100-N145 component was observed in Group 4 (patients with OD atrophy; 3.67±0.66 μV) vs. the control group (*P<0.05*) and Group 3 (P<*0.01*).

Table 2.

The parameters of the latency of the VEPs

Group	Visual acuity	The Oz-Cz derivation											
		The first channel						The second channel					
		N75 (ms)	deviation (%)	P100 (ms)	deviation (%)	N145 (ms)	deviation (%)	N75 (ms)	deviation (%)	P100 (ms)	deviation (%)	N145 (ms)	deviation (%)
Group 1	0.62 ±0.05	78.26 ±1.04	2.37 ±1.32	109.86 ±2.11	6.13 ±2.17	141.14 ±2.85	3.83 ±1.84	78.79 ±1.07	3.19 ±1.37	109.82 ±2.07	6.04 ±2.15	140.85 ±2.91	-3.97 ±1.88
	P2<0.001	*P1<0.05 P2>0.05*	*P2>0.05*	*P1<0.05 P2>0.05*	*P2>0.05*	*P1>0.05 P2>0.05*	*P2>0.05*	*P1>0.05 P2>0.05*	*P2>0.05*	*P1<0.05 P2>0.05*	*P2>0.05*	*P1>0.05 P2>0.05*	*P2>0.05*
Group 2	0.31 ±0.06	81.64 ±2.09	6.87 ±2.92	112.73 ±3.52	9.31 ±3.57	147.14 ±6.12	1.38 ±0.21	81.89 ±2.07	7.00 ±2.91	112.73 ±3.48	9.31 ±3.55	147.71 ±6.27	2.05 ±0.31
	P3>0.05	*P1<0.05 P3<0.01*	*P3<0.01*	*P1<0.05 P3<0.05*	*P3<0.05*	*P1>0.05 P3>0.05*	*P3>0.05*	*P1<0.05 P3<0.05*	*P3<0.01*	*P1<0.05 P3>0.05*	*P3<0.05*	*P1>0.05 P3>0.05*	*P3>0.05*
Group 3	0.22 ±0.04	93.14 ±3.57	23.72 ±4.92	123.65 ±3.93	21.13 ±3.85	154.84 ±4.91	6.58 ±3.38	92.75 ±3.90	23.49 ±5.23	123.37 ±4.06	20,60 ±4,05	155.29 ±4.83	6.95 ±3.34
	P4<0.001	*P1<0.05 P4>0.05*	*P4>0.05*	*P1<0.05 P4>0.05*	*P4>0.05*	*P1>0.05 P4>0.05*	*P4>0.05*	*P1<0.05 P4>0.05*	*P4>0.05*	*P1<0.05 P4>0.05*	*P4>0.05*	*P1>0.05 P4>0.05*	*P4>0.05*
Group 4	0.03 ±0.01	98.22 ±6.38	30.84 ±8.54	127.24 ±7.34	24.56 ±7.19	161.2 ±8.98	10.72 ±6.23	98.98 ±6.37	31.60 ±8.63	127.64 ±7.41	24.73 ±7.27	160.66 ±8.97	10.12 ±6.22
		P1<0.05		*P1<0.05*		*P1>0.05*		*P1<0.05*		*P1<0.05*		*P1>0.05*	
Control group	0.9±0.03	75.2±0.2		102±2.14		145±3.12		75±1.06		102±2.03		145±2.4	

P1 – vs. the control group; P2 – Group 1 vs. Group 2; P3 - Group 2 vs. Group 3; P4 - Group 3 vs. Group 4.

Table 3.

The parameters of the amplitude of the VEPs

Group	Visual acuity	The Oz-Cz derivation							
		The first channel				The second channel			
		N75-P100 (μV)	deviation (%)	P100-N145 (μV)	deviation (%)	N75-P100 (μV)	deviation (%)	P100-N145 (μV)	deviation (%)
Group 1	0.62±0.05	13.91±0.79	10.11±8.13	12.73±1.06	46.83±12.70	13.74±0.78	39.10±7.89	12.80±1.02	47.54±12.74
	P2<0.001	*P1<0.05 P2>0.05*	*P2<0.01*	*P1<0.05 P2>0.05*	*P2>0.05*	*P1<0.05 P2>0.05*	*P2>0.05*	*P1<0.05 P2>0.05*	*P2>0.05*
Group 2	0.34±0.06	15.77±1.29	61.39±12.95	13.31±0.94	54.60±11.20	15.92±1.24	61.6±12.77	13.34±0.92	57.09±10.83
	P3>0.05	*P1<0.05 P3<0.001*	*P3<0.001*	*P1<0.05 P3<0.001*	*P3<0.001*	*P1<0.05 P3<0.001*	*P3<0.001*	*P1<0.05 P3<0.001*	*P3<0.001*
Group 3	0.23±0.04	6.76±0.76	-29.00±7.34	7.54±0.83	-6.55±1.41	6.62±0.77	-30.43±7.60	7.07±0.71	-9.72±7.81
	P4<0.001	*P1<0.05 P4<0.01*	*P4<0.01*	*P1>0.05 P4<0.01*	*P4<0.001*	*P1<0.05 P4<0.01*	*P4<0.05*	*P1>0.05 P4<0.001*	*P4<0.01*
Group 4	0.03±0.01	3.68±0.46	-57.92±6.78	3.67±0.66	-49.00±9.85	3.60±0.49	-56.39±8.16	3.58±0.55	-52.47±8.81
		P1<0.05		*P1<0.05*		*P1<0.05*		*P1<0.05*	
Control group	0.9±0.03	9.8±0.63		8.4±0.42		9.8±0.36		8.4±0.27	

P1 – vs. the control group; P2 – Group 1 vs. Group 2; P3 - Group 2 vs. Group 3; P4 - Group 3 vs. Group 4.

Conclusion

The VEP parameters provide identification of the functional disorders of the optic nerve. Our results showed that there is delayed latency and reduced amplitude of the P100 and N75 components in patients with ischemic and atrophic stages of the disease. In ON, P100 was the most informative index. We noted that the N145 parameter in ON is not very informative. An estimation of VEP parameters provides a more reliable diagnosis of the stage of disease and aids in monitoring the effectiveness of treatment.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

Psychiatry and Addiction Medicine

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Clinical Manifestations of the Opiate Withdrawal Syndrome

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Abstract

Currently, substance abuse is one of the most serious problems facing our society. The aim of this study was to investigate the clinical manifestations of the opiate withdrawal syndrome (OWS). The study included 112 patients (57 women and 55 men) aged from 18 to 64 years with opium addiction according to the DSM-IV. To study the clinical manifestation of OWS, the special 25-score scale with four sections to assess severity of sleep disorders, pain syndrome, autonomic disorders, and affective symptoms was used. Given the diversity of the OWS symptoms, attention was focused on three clinical variants, affective, algic and mixed. The OWS affective variant was registered more frequently in women, while the mixed type of OWS was more typical of men. **(Int J Biomed. 2015;5(3):151-154.)**

Key words: *Opiate withdrawal syndrome (OWS); OWS 25-score scale.*

Introduction

Currently, substance abuse is one of the most serious problems facing our society. A wide diversity of clinical signs and symptoms of substance abuse contributes to the development of novel diagnostic and therapeutic strategies [1, 2, 3]. Full-value treatment of opioid addicts depends on rapid and successful coping with withdrawal disorders. Clinical picture of the opiate withdrawal syndrome (OWS) involves a constellation of symptoms. Typically OWS presents concurrently as several of the following signs: algesic, autonomic, emotional, sleep, psychopathic, hypochondriac, and other disorders [4, 5]. Peculiar bothersome sensations localizing in muscles, joints, skin, and other parts of body are the most torturous symptoms. These sensations are close to the painful feelings, but at the same time they differ from them, resembling senestopathies [6]. Accompanied by specific autonomic disorders, such as chill, sweating, rhinorrhea, dry mouth, and nausea, these sensations cause disproportionately potent emotional response with prevailing depressive-hypochondriac and dysphoric symptoms [7, 8].

T. Galaktionova [9] studied a syndrome-based structure of the acute conditions in opiate addicts and proposed a classification, which distinguishes the algic (pain), mixed, and affective forms of OWS. This classification, which is very handy for physicians, directly associates the algic (pain) and mixed forms with the pain and autonomic syndromes; while the emotional lability, irritability, low mood, anxiety and dysphoria can be seen in the clinical structure of the affective syndrome of OWS. The identification of the main symptoms and their removal determines the successful treatment strategy for OWS. Successful treatment of OWS is the subject of great therapeutic efforts.

The aim of this study was to investigate the clinical manifestations of the opiate withdrawal syndrome.

Materials and methods

The study included 112 patients (57 women and 55 men) aged from 18 to 64 years with opium addiction according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), 2000) [10]. The study included patients who voluntarily sought treatment for opioid dependence and was performed at the Republican addiction treatment center (Tashkent, the Republic of Uzbekistan) during 2010 to 2014. All patients underwent detoxification (no more than 20 days) and had to be off opiates for at least 7 days before the study.

The mean age of women was 32.9±8.6 years (*Me* 32 years; IQR 27.0-36.0), and of men it was 35.7±5.8 years (*Me* 36 years; IQR 31.5-39.0). The exclusion criteria were as follows: mental derangements in addition to drug addiction, a lack of follow-up information, mixing heroin with other drugs, and heroin use as a substitution for other psychoactive substances.

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The study was approved by the independent ethic committee and conducted in accordance with good clinical practice guidelines and the World Medical Association Declaration of Helsinki. Written *i*nformed consent was obtained from each patient.

The mean age of substance use onset at the moment of primary examination was 24.6±6.7 years (*Me* 23.0 years; IQR 19.0-29.0); the duration of heroin abuse ranged from 2 months to 23 years (9.5±5.1 years; *Me* 9.5 years; IQR 5.0-13.0). The vast majority of the patients have used heroin for less than 12 years (67.9% vs. 32.1%; OR=4.46; 95% CI:2.54–7.81; *P=0.000*). The majority of patients (82.1%) used heroin intravenously.

To study the clinical manifestation of OWS, we have used a special 20-score scale developed by M. Treschinskaya and V. Khrykin [11]. This scale includes three sections to assess the severity of sleep disorders (including agrypnia), pain syndrome, and autonomic manifestations. In our modification, this scale has been supplemented by new section to assess the affective variant of OWS. Thus, the final scale consisted of 25 items designed to assess the severity of OWS. A five-score subscale is used to assess severity of sleep disorders (Section 1) ranging from 1 score for sleep less than one hour a night to 5 scores for a duration of sleep more than 7 or 8 hours. Similar maximum generalized 5-score subscale is intended for assessment of pain syndrome severity (Section 2). Autonomic disorders (Section 3) are assessed by three subsections. Thus, a 4-score subscale is used to assess intestine dysfunction severity, a 3-score subscale serves to monitor changes in salivation, and a 3-score subscale is intended for assessment of rhinorrhea. The last 5-score subscale serves to assess the affective manifestation (Section 4). This questionnaire for assessment of the OWS severity (Table 1) is filled in by a doctor in charge for each patient.

Table 1.
Questionnaire for assessment of the OWS severity

Clinical parameters of OWS	Score	Clinical parameters of AWS	Score
1. Sleep and sleep disorders Sleep duration		Loose stool 4-5 times a day	2
7-8 and more hours a day	5	Loose stool more than 5 times a day	1
Under 7 hours	4	B. Salivation	
Under 5 hours	3	Normal	3
Under 3 hours	2	Moderately high	2
Less than 1 hour a day	1	Acutely high	1
2. Pain syndrome		C. Rhinorrhea	
No manifestations	5	No manifestations	3
Mild	4	Moderate	2
Moderate	3	Severe	1
Severe	2	4. Affective syndrome	
Severest	1	Emotional lability	5
3. Autonomic disorders		Irritability	4
A. Intestine dysfunctions		Feeling low, anxiety	3
No diarrhea (solid stool 1-2 times a day)	4	Dysphoria	2
Soft or loose stool 2-3 times a day	3	Psychomotor excitation	1
Total score _____			

Affective syndrome with concurrent emotional lability, irritability, low mood and anxiety scores 5, 4 and 3, respectively; the one with dysphoria or psychomotor excitation scores 2. To assess severity of affective syndrome only leading symptom is set aside. The total sum of scores is used to interpret the parameters of OWS scale. Thus, the total sum of scores ranging from 22 to 25 indicates a mild OWS and a patient's compensated condition, one ranging from 16 to 21 reflects a moderate compensated OWS. Range of 13-15 scores indicates a marked compensated AWS, the one of 12-17 scores reflects a compensated highly marked OWS; the total sum of scores less than 7 is the evidence for the decompensated OWS. On the basis of the scores we can determine the OWS variant as affective, algic or the mixed one, which takes an intermediate position between affective and algic one.

All data were processed by means of STATISTICA 6 and BIOSTAT software packet. Quantitative parameters are presented as M±SD, Median (*Me)*, and 25th and 75th percentiles (IQR, Inter Quartile Range). Odds ratio (OR) with 95% confidence interval (CI) was calculated for each factor. Statistical significance of differences between parameters in the sample was assessed by means of non-parametric $\chi 2$ test (Pearson's criterion). Minimum significance was set at $P \leq 0.05$.

Results

Given the diversity of the OWS symptoms, we focused on three following clinical variants.

OWS affective variant was registered in 42 (37.5%) patients, 29 (69.0%) women and 13 (23.6%) men among them. In this group of patients an algic or pain component was found mild scoring 3.4±0.7; seem to be minor for the patients autonomic symptoms scoring 7.3±1.3 were found insignificant. More than half of patients with the OWS affective variant (57.1%) actively and sometimes importunately complained of embarrassment, anxious expectation, and foreboding of evil. Affective component was the marked one (scoring 2.5±0.7) manifesting in anxiety (in 57.1%) and dysphoria (in 31.0%); psycho-motor excitation was registered more rarely (in 9.5%) (Table 2). Sleep disorders scored 3.1±0.8. This variant was registered significantly more frequently among women than among men (OR=4.98; 95% CI: 1.97-12.6; *P=0.001*).

AWS algic variant was observed in 35 (31.2%) patients, 16 (45.7%) women and 19 (54.3%) men among them. These patients within post-withdrawal period complained of dragging and twisting pain in the lumbar region, knee joints, and gastrocnemius muscles. The OWS algic component scored 2.6±0.7. In this group most patients (71.4%) described unusual, peculiar and bothersome sensations characterizing them as "tearing flesh off the bones", "twisting of joints", "itching bones"; some mentioned a flu-like twisting body pain. The sensations above, particularly, those of high intensity were accompanied by a patient's fussiness and restlessness; the patient needed to change position of his/her body once and again. At the same time, patients complained of a chill followed by a fever; salivation, lacrimation, and sneezing took place. In this group of patients, the autonomic component scored 6.6 ±1.4, affective one was mild scoring 3.4±0.7. Sleep

disorders were also typical for the patients with this OWS variant, scoring 3.0±0.9. The frequency of this AWS variant among women and men was similar (OR=0.71; 95% CI: 0.28-1.82; *P=0.63*)

AWS mixed variant taking an intermediate position between the OWS affective and algic variants was found in 35 (31.2%) patients, 12 (34.3%) women and 23 (65.7%) men among them. This group of patients comprised those with algic, autonomic and affective disorders scoring 3.2±0.7, 7.4±1.3 and 3.01±0.7, respectively; that is, presentation of the disorders in the OWS clinical picture was almost equal. These patients complained of unwellness, embarrassment and bothersome sensations poorly localized in the body; these numerous complaints were undifferentiated. Requiring greater attention from others, the patients were cranky and bad tempered. Sleep disorders in this group of patients were less severe than in those with algic variant, and scored 3.4±0.7. This variant of OWS was registered in men more frequently than in women (OR=3.67; 95% CI: 1.36-9.89;*P=0.02*).

Table 2.
Parameters of the OWS severity

Clinical parameters of OWS	OWS variants					
	affective n=42		algic n=35		mixed n=35	
	n	%	n	%	n	%
1. Sleep and sleep disorders. Sleep duration						
7-8 or more hours a day	-	-	1	2.9	-	-
Under 7 hours	13	31.0	11	31.4	19	54.3
Under 5 hours	22	52.4	11	31.4	13	37.1
Under 3 hours	7	16.7	12	34.3	3	8.6
Less than 1 hour a day	-	-	-	-	-	-
2. Pain syndrome						
No manifestations	-	-	-	-	-	-
Mild	23	54.8	3	8.6	10	28.6
Moderate	15	35.7	17	48.6	22	62.9
Severe	4	9.5	14	40.0	2	5.7
Severest	-	-	1	2.9	1	2.9
3. Autonomic disorders						
A. Intestine dysfunctions						
No diarrhea (solid stool 1-2 times a day)	3	7.1	3	8.6	4	11.4
Soft or loose stool 2-3 a day	23	54.8	13	37.1	20	57.1
Loose stool 4-5 times a day	16	38.1	15	42.9	10	28.6
Loose stool more than 5 times a day	-	-	4	11.4	1	2.9
B. Salivation						
Normal	13	31.0	3	8.6	9	25.7
Moderately high	27	64.3	30	85.7	25	71.4
Acutely high	2	4.8	2	5.7	1	2.9
C. Rhinorrhea						
No manifestations	14	33.3	9	25.7	13	37.1
Moderate	28	66.7	23	65.7	22	62.9
Severe	-	-	3	8.6	-	-
4. Affective syndrome						
Emotional lability	-	-	1	2.9	-	-
Irritability	-	-	15	42.9	10	28.6
Feeling low, anxiety	25	59.5	18	51.4	22	62.9
Dysphoria	13	31.0	-	-	1	2.9
Psychomotor excitation	4	9.5	1	2.9	2	5.7

Discussion

The findings from our study confirm some authors' opinion concerning presence of some variants in OWS, to name affective, algic and mixed [9, 12, 13]. In our study sleep disorders of similar intensity could be seen in all three variants, autonomic symptoms were more pronounced in algic one. K.Mosikyan [12] concludes that clinical parameters underlying the formation of opium addiction as well as presence of concurrent psychic pathology determine formation of clinical variant of opium withdrawal syndrome. Affective variant of opium withdrawal syndrome is typical of persons with unstable type of premorbid personality, moderately progressive course of addiction and short duration of substance abuse.

Since OWS affective variant in our study was registered more frequently among women than among men and the mixed one was typical of male opium addicts, it is possible to speak of gender peculiarities in the clinical picture of OWS. Opium abuse duration was found not to influence OWS variant. Previously, gender peculiarities were found in the type of opium abuse course [14].

Conclusions

Clinical picture of acute withdrawal syndrome has been proved to be diverse. In our study we observed some OWS clinical variants with peculiarities significant for diagnosis and treatment strategy. It is of importance that OWS affective variant was registered more frequently in women, while the mixed type of acute withdrawal syndrome was more typical of men. We believe that these features taken into account would help improve the effectiveness of opioid addiction treatment.

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ORIGINAL ARTICLE

Plant physiology and biochemistry

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Lipid Profiles are Altered in Rats Fed with Different Garlic Cultivars

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Abstract

Garlic has antioxidant and hypocholesterolemic properties that are attributed to its organosulfur compounds being allicin, which is reported to be the most active of these compounds. We hypothesized that allicin content could reduce plasma concentrations of triglycerides (TG), total cholesterol (TC), HDL (high density lipoproteins), VLDL (very low density lipoproteins), and glucose. Two different cultivars of commercial garlic, Peruano and Jinxiang, were used. Thirty male Wistar rats were distributed into 6 groups and fed for 15 days with standard diet (Control), Control with Peruano garlic treatment (CGP), Control with Jinxiang garlic treatment (CGCH), cholesterol-added control diet (CholC), cholesterol-added diet with Peruano garlic treatment (CholGP), and cholesterol-added diet with Jinxiang garlic treatment (CholGCH). Garlic treatment consisted of a daily oral dose of 1ml of lyophilized garlic. We observed that garlic treatment in Control group significantly reduced plasma TG and VLDL concentrations. The CGCH group presented a significant increase in plasma TC levels (25.5%) and glucose (11%). No significant changes in TC, HDL, TG and VLDL were observed in CholGP and CholGCH, but levels of fasting plasma glucose were increased: CholGP (23%) and CholGCH (27.5%). Results suggested allicin treatments alter lipid profile in rats. Nevertheless, further studies are necessary to address the increase in plasma glucose levels. **(Int J Biomed. 2015;5(3):155-161.)**

Keywords: *powder garlic; allicin; rats; cholesterol; fasting plasma glucose.*

Abbreviations

TC, total cholesterol; **HDL**, high density lipoprotein; **VLDL**, very low density lipoprotein; **TG**, triglycerides; **Control**, standard diet; **CGP**, Control with Peruano garlic treatment; **CGCH**, Control with Jinxiang garlic treatment; **CholC**, cholesterol added control diet; **CholGP**, cholesterol-added diet with Peruano garlic treatment; **CholGCH**, cholesterol-added diet with Jinxiang garlic treatment; **OSC**, organosulfur compound; **CVD**, cardiovascular disease.

Introduction

Garlic contains 33 organosulfur compounds (OSC), 17 amino acids (including all essential amino acids), minerals such as phosphorus, calcium, iron, potassium, magnesium, selenium, zinc, and vitamins A, B, C, and E [1]. This bulb and its preparations have been widely recognized as an agent capable of preventing and treating cardiovascular diseases (CVD), atherosclerosis, thrombosis, hypertension, and diabetes [2,3]. It has been suggested that garlic's beneficial properties are attributed to specific OSC, including sulphoxides and γ-glutamil peptides that are present in the crude clove [4,5].

Allicin (diallylthiosulfinate), a volatile liquid, is responsible for the pungent odor of garlic, representing approximately 70% of all thiosulfinates present in the crushed clove [6]. The compound is not found in intact plants, but it is formed by action of the enzyme named alliinase (EC4.4.1.4), derived from a non-proteinogenic amino acid *S*-allylcysteine *S*-oxide (aliin) at the time garlic is crushed [7]. In garlic powder the conversion of aliin to allicin begins when water is added to the powder, being quickly degraded into diallyl disulfide (DADS), vinyldithiins and ajoenes [8].

Atherosclerosis is one of the highest risk factor in hypertension development and CVD [9]. CVD are the main causes of death among the Western population. Risk of CVD is higher in men than in women who are in the pre-menopausal

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period. Multiple factors contribute to its development, such as lifestyle (smoking, physical inactivity, etc.) and stress. High levels of cholesterol in the plasma, particularly LDL and TG, are associated with an increase in CVD risk [10]. Oxidative change of LDL by reactive oxidative specie (ROS) is also considered an important mechanism in atherosclerosis and hypertension [10,11]. The cardio protector effect of garlic has been extensively assessed. Several in vitro studies have indicated that garlic and its components inhibit the key enzyme HMG-CoA reductase (*3-hydroxi-3 methylglutaryl Coenzime A*), which is associated with cholesterol and fatty acids synthesis [12-14]. In different assays carried out with animals, garlic extracts showed the ability to reduce cholesterol and lipid levels in the blood plasma of rats [15,16]. In humans, garlic significantly reduced plasma lipids levels, especially TC and LDL [17,18]. However, studies continue to be conducted due to the differences found. Active components of raw garlic may vary according to cultivar, harvest, and storage conditions. Various garlic preparations have been used in different studies. However, there is a lack in the literature concerning which are the most important active ingredients and how they impact lipid metabolism. Given this scenario, we hypothesized that the amount of allicin present in garlic could reduce the plasma concentration of TG, TC, HDL, VLDL, and glucose. To test our hypothesis we used an animal model and two commercial cultivars of garlic, Peruano and Jinxiang, grown in Brazil and China, respectively, which were submitted to a lyophilized process in order to preserve their properties and facilitate handling of the garlic throughout the experiment. This study aimed to: (a) assess the content of allicin in garlic cultivars (Peruano and Jinxiang), commercially available in the local market and (b) study the effect of allicin levels in reducing plasma concentrations of TG, TC, HDL, VLDL and plasma glucose in animals fed with either standard or cholesterol-added diets.

Material and Methods

1. Garlic processing

Bulbs of fresh garlic (*Allium sativum* L.), cultivar Peruano, were obtained from commercial and experimental fields in Brasília, DF, Brazil. Bulbs were harvested 150 days after planting and submitted to curing. Bulbs from Jinxiang cultivar, imported from China, were obtained at the local wholesale market. Fresh and healthy bulbs were selected and graded. Garlic cloves were manually stripped without harming the product, using a kitchen knife. Then they were frozen at a temperature of -70±1°C for approximately 8 hours, using an ultra-freezer (ULT1386-5-D40, Revco, Illinois, USA), sliced in an industrial processor (CL50, Robot Coupe, USA) with 5mm thickness and immediately lyophilized (LS3000, Terroni, São Carlos, Brazil) for approximately 3 days. The product was then crushed in a knife mill (SL31, Solab, Piracicaba, Brazil), and put in sealed polyethylene bags.

2. Allicin content determination

Allicin content was determined according to the Institute for Nutraceutical Advancement 110.001 method INA [19]. Analyses were performed by a reversed phase, high-performance liquid chromatography (RP-HPLC) system (Shimadzu, Japan). Oven temperature was set at 28±0.5°C. Samples were eluted with methanol and water (50:50 v/v), using a flow of 1.0mL/min for 20 minutes and detected at 240 nm. Injection volume was 25 µL. Allicin determination was performed comparing the area under the peak produced by the aqueous extract of garlic to a standard peak of allicin. Allicin standard solution was obtained by the oxidation of *diallyl disulfide,* according to Lawson & Wang [20]. Allicin concentration (C) in the solution was calculated according to Eq.:

$$E_{1cm}^{1\%} = \frac{Absorbance}{C(\mu g/mL)} x10000 \quad , \textit{in which:}$$

E=extinction coefficient for allicin in water (145.4, considering a cell of 1 cm of wavelength of 240 nm).

A standard curve was obtained by subsequent dilutions (5, 10, 15, 20, 30, 40, 50, 60, 70 and 80 µg/mL) of the standard solution. To determine allicin content, lyophilized garlic powder was reconstituted with water. Samples of 0.4 g of garlic powder were placed in 50 mL plastic tubes, 10mL of deionized water was added at room temperature and tubes were sealed using plastic film (Parafilm). Samples were homogenized using a tube agitator (IKA®, model MS1, German) and left at room temperature for approximately 6 minutes in order to produce OSC. Then samples were filtered through a filtrating membrane of 0.45 µm (Millipore, USA) and transferred to an HPLC vial.

3. Animals and diets

The Institute of Biological Sciences/University of Brasilia (Brasilia, DF, Brazil), Ethical Committee for Animal Research approved all the adopted procedures (Protocol CEUA/ICB/UnB no. 18914). Wistar male rats (n=30) approximately 7 weeks old, used in the present study, were obtained from the Institute of Biological Sciences of University of Brasília. For 15 days, the animals were individually kept in polypropylene boxes in the following conditions: 23±2°C, 50%–60% relative humidity, and a photoperiod of 12 hours. All animals had free access to food and water. All experimental diets were distributed in a pellet form, based on the diet for growing rodents of the American Institute of Nutrition (AIN)-93G. After adaptation for one week, animals were randomly distributed in 6 groups of 5 animals each. Group 1 received the standard diet (Control). Groups 2 (CGP) and 3 (CGCH) received the same diet as Group 1, with the addition of Peruano garlic (Group 2) and Jinxiang garlic (Group 3). Group 4 (CholC) received a cholesterol-based diet, containing 0.125% of sodium cholate and 0.5% of cholesterol (Control containing cholesterol), according to the model of Yanagita et al [21]. Groups 5 (CholGP) and 6 (CholGCH) received the same diet as Group 4, with Peruano garlic (Group 5) and Jinxiang garlic (Group 6) added (Table 1).

3.1. Samples preparation for garlic treatment

Lyophilized garlic powder was daily reconstituted with water and fed to the animals at the same time, in the morning, before the regular diet. The quantity was equivalent to 500

mg of lyophilized garlic/kg of the animals' body mass [22]. Garlic powder was added with 1 mL of filtered water at room temperature, homogenized and left at the counter top for 6 minutes to yield OSC. Then rehydrated garlic was fed to animals by gavage. Each animal of every group (CGP, CGCH, CholGP and CholGCH) received 1 mL of reconstituted garlic and the other groups (Control and CholC) received 1mL of physiologic saline solution, once a day. During the experiment, garlic doses were adjusted according to the mass increase of the experimental animals.

Table 1.
Composition of experimental diets (g/Kg)

Ingredients	Control	CGP/ CGCH	CholC	CholGP/ CholCH
Cornstarch†	529.49	524.49	523.24	518.24
Casein (≥ 85% of protein) †	200	200	200	200
Sucrose‡	100	100	100	100
L-cystine†	3	3	3	3
Soybean oil§	70	70	70	70
Microcrystalline cellulose †	50	50	50	50
Mineral mixture - AIN93G†	35	35	35	35
Vitamin mixture - AIN93G†	10	10	10	10
Choline bitartrate †	2.5	2.5	2.5	2.5
Tert-butylhydroquinone£	0.014	0.014	0.04	0.014
Cholesterol£	-	-	5	5
Sodium cholate£	-	-	1.25	1.25
Lyophilized garlic	-	5	-	5

Tested diets were formulated based on the diet AIN-93G.
† Rhoster Indústria e Comércio Ltda (Vargem Grande Paulista, SP, Brazil).
‡ Vetec Química Fina (SP, Brazil).
§ Refinações de Milho Brasil
£ Sigma Chemical Co.(St Louis, MO, USA).

4. Data collection

Rats were daily monitored and individually weighed every 2 days and before blood collection at the end of the experiment. Their daily food ingestion and weight increments were registered during the experimental period.

5. Blood collection

Blood samples of each individual rat were collected at the end of the experiment with animals having fasted for 12 hours. Rats were anesthetized by the intraperitoneal route with quetamine association (100 mg/Kg) and xilazine (10 mg/Kg). Blood collection was performed by cardiac punction. The animals' euthanasia was performed with an overdose of barbiturics. Blood was collected using sterilized syringes and needles and immediately transferred to dry hemolysis tubes with cap, stored in an ice bath, and taken for biochemical processing a maximum of 1 hour after collection. Plasma was separated using a centrifuge (SIGMA, 2-5, Osterode am Harz, Germany) at 1200*g*, for 10 minutes, at room temperature.

6. Enzymatic analysis

TC, HDL, TG and glucose were assessed using an enzymatic analytical kit from Abbott Laboratories (Illinois, USA) in automated equipment (ARCHITECT C8000, USA). VLDL fraction was calculated according to the following equation: VLDL=(Trygliceride/5) used for triglyceride values < 400 mg/dL [23].

Statistical analysis: Results were expressed by mean±SD. Data were subjected to the chi-square test with 5% of probability, with the purpose of checking population adherence to the normal distribution curve. As there was no population adjustment to normal distribution, the non-parametric method of analysis using Kruskal Wallis test (P<.05) was chosen.

Results

1. Allicin content

No significant differences in allicin content for fresh Peruano and Jinxiang garlics were observed. However, significant differences were verified when these varieties were lyophilized. The lyophilization process caused a significant reduction in allicin content for the Jinxiang cultivar (91%) (Table 2).

Table 2.

Allicin content in the samples of aqueous extract of crude garlic and after lyophilization processing

Cultivars	Crude Garlic*		Lyophilized garlic *
	mg/g FM product	mg/g DM product	mg/g DM product
Peruano	7.90 ± 0.09 [a]	21.95 ± 2.65 [a]	27.04 ± 0.32 [a]
Jinxiang	6.73 ± 0.03 [a]	20.04 ± 0.49 [a]	1.88 ± 0.26 [b]

** [a,b] Means in the same column, followed by different letters, are statistically different among them at the level of 5 % (P< 0.05). FM = fresh matter and DM = dry matter.*

Jinxiang garlic was included in the present study once it was imported from China, and it was not possible to define all postharvest procedures until it reached the final market. On the other hand, Peruano garlic is grown locally and all the postharvest steps are known. These differences are probably associated with the observed distinct levels of allicin. Our study also showed that garlic variety influenced allicin during the lyophilization process.

2. In vivo experiment

Garlic treatment in the standard diets and cholesterol-based diets influenced the body weight of experimental animals (Table 3).

Table 3.

Effect of lyophilized powder garlic in standard diets and cholesterol added diets in relation to body weight, (g) weight gain (%) and consumption of feed (g/day) in the rats groups

Study Group	Body weight 1st day*	Body weight 15th day*	Body gain	Feed consumption
Control	184.17 ± 12.36 [a]	267.43 ± 18.30 [a]	45.34 [ba]	32.25 ± 2.66 [ca]
CGP	172.17 ± 12.09 [a]	222.56 ± 7.57 [b]	29.58 [b]	26.65 ± 1.56 [dc]
CGCH	179.05 ± 8.61 [a]	264.14 ± 15.09 [a]	47.93 [ba]	30.98 ± 3.72 [ca]
CholC	177.66 ± 3.17 [a]	267.41 ± 5.13 [a]	50.53 [ba]	33.22 ± 2.15 [a]
CholGP	165.88 ± 11.39 [a]	218.46 ± 6.19 [b]	32.24 [b]	24.32 ± 0.51 [db]
CholGCH	173.34 ± 8.06 [a]	284.84 ± 10.34 [a]	64.42 [a]	32.16 ± 1.31 [a]

Results expressed as mean ± SD.
[ba] Different letters, in a same column, and in different assays, indicate a significant difference (P <0.05).

Rats that were treated with Peruano garlic (CGP and CholGP) showed lower body weight, lower increment in body weight after 15 days of study, and consumed lower amounts of feed compared to other groups. However, there were no statistical differences in body weight, weight increment, and feed consumption for the CholC group in relation to the Control group.

We verified similar trends in the CGP group, fed with 13.52 mg of allicin/kg of animal mass, to the study conducted by Elkayam et al [24]. Other studies conducted by Lee et al.[25] and Sohn et al. [9], both with diets enriched with garlic powder, did not show any change in food intake and in weight gain.

Our results showed that garlic can help in weight loss by reducing the appetite (Table 3). The possible mechanism of appetite reduction is probably associated with the strong odor of garlic, which stimulates the brain satiety center, reducing the desire to eat. It is still believed that garlic can stimulate the nervous system to release hormones such as adrenalin, which can accelerate the metabolic rate, helping in losing weight [26]. As Peruano garlic has higher amounts of allicin, it consequently has a more pungent odor, generating a stronger stimulus in the brain and, thus, accelerating metabolic rate.

Changes in lipid concentration in blood plasma after 15 days are shown in Figure 1. Group CGP kept cholesterol levels similar to the Control group, whereas the CholGCH group showed a significant increase (25.5%). Rats fed with the cholesterol-based diet presented a significant increase in cholesterol levels in blood plasma when compared to the group fed with a standard diet. Groups CholGP and CholGCH did not present significant differences in relation to the CholC group.

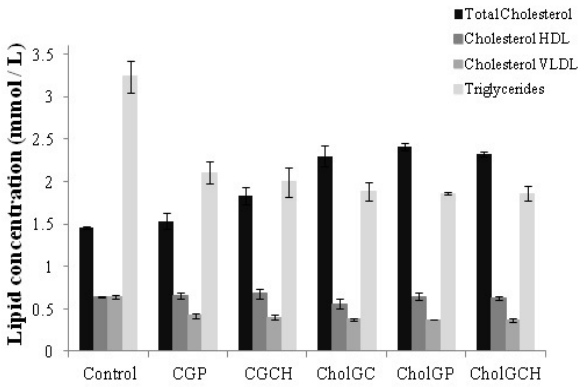

Fig. 1. *Changes in lipid levels in blood plasma of rats fed with a diet either with or without cholesterol. Values are means. Vertical bars represent standard deviation.*

Glucose levels in the plasma were altered due to different diets (Fig. 2). There was a significant increase in the CGCH group when compared to Control, as well as for CholGP and CholGCH when compared to CholC and Control. Therefore, in a standard diet, CGCH garlic consumption can increase the glucose level in the blood, as well as in CholGP and CholGCH.

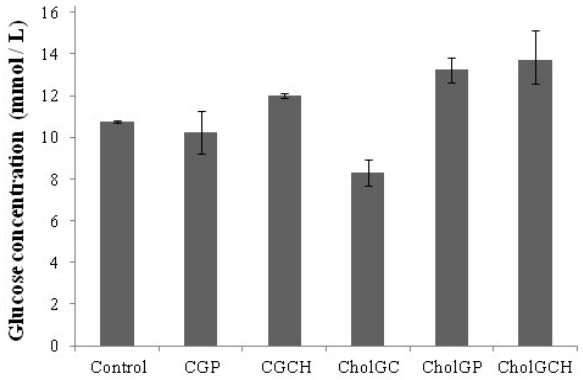

Fig. 2. *Changes in glucose levels in blood plasma of rats fed with a diet either with or without cholesterol. Values are means. Vertical bars represent standard deviation.*

Discussion

The observed difference is probably associated with allicin instability, which can vary during the process and with different cultivars [27,28]. Lawson and Hughes found 7.52 mg/g of allicin in garlic powder, dried in slices with 3 mm thickness at 60°C for approximately 57 hours, followed by spraying using a mill. Garlic powder extract was obtained by adding water (20 mL/g) and incubating at 23°C for 8 minutes, followed by filtration and evaluation with HPLC (240 nm and mobile phase of 50% of methanol in water). In the same study carried out by Lawson and Hughes [29], authors assessed the production of thiosulfinates during the garlic drying process. The amount of allicin formed in the fresh product was around 12.1 mg/g (dry weight) and the garlic powder was 11.6 mg/g(dry weight). Loss caused by the drying procedure was nearly 4%. In our study, we observed higher values either in fresh product or in garlic powder. According to Calín-Sánchez et al. [30], different drying methods can alter the final results, as one could expect. Garlic homogenization by spray-drier results in aliinase loss of activity, the same occurring with drying methods that use very high temperatures. Drying in low temperatures (<60°C) has minor effects on the production of main thiosulfinates (allicin and alil methyl thiosulfinates). We also noticed that garlic cultivars influenced the activity loss of aliinase.

In another study, Lawson et al. [31] assessed different thiosulfinates, including allicin, present in tablets of garlic powder marketed in Australia, Germany, the USA and Japan. The amount found corresponded to 3.60mg/g product (Australia); 3.10 mg/g product (USA); 0.26 to 2.55 mg/g product (Germany) and not detected (Japan). According to the authors, this wide range was due to different procedures used to prepare garlic powder, which has a potential to preserve the releasing capacity of allicin in garlic. However, while some garlic powders release a significant amount of allicin when in contact with water, many do not indicate any variation. Therefore, it is possible to observe variations in allicin content depending on garlic powder processing [32-34].

Future studies should address different processes to

minimize allicin reduction during the drying process, searching for the best drying process for each cultivar, besides assessing possible formation of other organosulfur compounds and their effects in experimental animals.

Results of the present study associated with the CholGP group were similar to the ones observed in the investigation conducted by Chi at al. [35], in which rats fed with 1% of cholesterol, 15% of pig fat, and supplemented with 2% (320 mg/day) and 4% (640 mg/day) of garlic powder for 4 weeks, presented a significant reduction in feed ingestion and weight gain in the group with the cholesterol-based diet supplemented with 2% garlic.

Findings of the present investigation regarding cholesterol levels for the CGP group are in line with the results verified by Gorinstein et al. [21]. These researchers observed that rats fed with a standard diet supplemented with 25 mg of lyophilized garlic powder, equivalent to 500 mg of fresh garlic/kg of body weight, for 4 weeks did not present significant differences in relation to control. For the groups CholGP and CholGCH, our results were similar to the ones observed by Asdaq [36].

On the other hand, other studies verified results that are the opposite of ours. Aouadi et al. [37] observed that supplementing the standard diet with 10% fresh garlic (equivalent to 2%–3% of garlic powder) reduced plasma cholesterol in 12.2% of subjects. The study conducted by Ali et al.[38] showed a reduction of 35% in plasma cholesterol in a high cholesterol diet (2%) when rats were supplemented with 50 mg of garlic powder/kg animal weight, containing 0.6% of allicin. Chi et al. [35] verified a reduction in plasma cholesterol of 45.5% and 44% in rats fed with a diet containing 1% of cholesterol and supplemented with 2% and 4% of lyophilized garlic powder, respectively.

Although our data suggest an increase in HDL levels in the standard diets with garlic treatment, differences observed among treatments were not significant. Other studies verified similar results [13,39].

There was a significant reduction in VLDL and TG serum concentrations for rats of groups CGP, CGCH, CholC, CholGP, and CholGCH when compared to Control. Reduction for the studied groups in both analyzed concentrations was: 35% for CGP, 38% for CGCH, 42% for CholC, CholGP and CholGCH. No significant differences were verified for VLDL and TG levels among the cholesterol-based diets. The present study showed that garlic treatments in a standard diet significantly reduced TG and VLDL concentrations in rats' plasma. Other studies showed a reduction in TG concentrations [40]. However, in general, many studies showed changes in TG and VLDL levels when standard diets, with moderate to high levels of cholesterol, were supplemented with garlic [41,29].

High levels of TG in the serum are associated with pathogenic conditions that accelerate atherosclerosis, such as insulin resistance and low levels of HDL [42]. Consequently, garlic consumption by groups CGP and CGCH can reduce the risk of cardiovascular diseases due to the reduction of TG and VLDL levels.

The effect of garlic in glucose concentrations was not addressed significantly in the searched literature, and the studies carried out had inconsistent results. Chi et al. [35] and Seo et al. [43] showed a significant reduction in glucose levels in rats fed with a high content cholesterol diet supplemented with garlic powder.

Thomson et al. [40] showed in a study that aqueous extract of fresh garlic ingested in small quantities (50mg/kg) reduces the concentration of cholesterol and triglyceride and does not alter the glucose level in the plasma. However, the study found that high doses of garlic (500mg/kg) would reduce plasma glucose levels, which is different from the results verified in this study.

The effect of garlic, and especially allicin, on the lipid profile has been the object of many controversies in animal models, since there is no standardization for the garlic concentration used. There are papers that have mentioned the protective effect to health of fresh garlic but not allicin, since they use garlic as the study base. There are several methods of preparing garlic and, specifically for garlic powder, there are several ways to process it, which implies variation in allicin content. The duration of the experiment duration is also questionable; many studies already published have shown different assessment times. Garlic cultivars present variable results *in vitro* which can generate differences in the *in vivo* results. All these facts, among others not mentioned, can explain the differences presented in our study regarding the literature data on TC, HDL, VLDL, TG and glucose levels in the plasma of experimented animals.

Concerning garlic ingestion, a significant part of the worldwide population consumes garlic as a condiment in their usual meal, without a defined quantity. The effective dose of garlic has not been determined; however, clinical studies in humans have shown that the ingestion of 4 to 6g of garlic powder/day is considered safe when done in a meal [44]. Our results are within the range of these values, after extrapolation of the animal dose of 500mg of garlic powder/kg of the animal weight. This amount corresponds to 4.86g of garlic powder for one person with 60kg, according to the Food and Drug Administration [45].

Conclusions

The present study showed differences in allicin content between two garlic cultivars assessed after a lyophilization process. We also observed differences in the *in vivo* results, probably due to the differences verified for allicin content. The ingestion of Peruano garlic reduced TG and VLDL levels in blood plasma of animals fed with a standard diet. These results indicate that this cultivar might have an important role in the prevention of atherosclerosis. On the other hand, although Jinxiang garlic consumption reduced TG and VLDL levels, it increased TC levels in 25.5% of the animals kept on a standard diet and increased glucose levels 12% and 27.5% in those on standard diets and cholesterol-based diets, respectively. Thus, this cultivar can present a risk factor for diabetes and it is not recommended to be used as a lyophilized product, in the conditions under which the present study was carried out. Our work is, to the best of our knowledge, the first to show

that garlic powder can significantly affect the levels of plasma glucose. Thus, it should be monitored periodically to identify, in future studies, possible mechanisms associated with this increment. For consumption of fresh garlic, additional studies should focus on how these cultivars can contribute to the reduction of the parameters (CT, LDL, VLDL and TG) associated with CVD.

Competing interests

The authors declare that they have no competing interests.

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CASE REPORT

Surgery

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Laparoscopic Sleeve Gastrectomy Complicated by Mesenteric Vein Thrombosis, Abdominal Compartment Syndrome and Pulmonary Emboli: Case Report

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Abstract

Background: Obesity is a growing problem all over the world, including the United States. Single-incision laparoscopic sleeve gastrectomy is a surgery performed for patients who want to lose weight. The number of deaths resulting from thromboembolic complications from bariatric surgeries continues to be of major concern.

Case Description: A 38-year-old female was admitted for single incision sleeve gastrectomy and was discharged home three days later. Subsequently she began to have abdominal pain, nausea and vomiting. A CT scan revealed superior mesenteric vein thrombosis with small bowel ischemia, splenic infarction and main and right portal vein branch thrombosis. An exploratory laparotomy demonstrated necrotic bowel due to abdominal compartment syndrome, and an area of small bowel was resected due to internal hernia. Surgical management of the patient during her second hospital stay included a decompressive laparotomy, internal hernia reduction, a small bowel resection.

Discussion: Superior mesenteric vein thrombosis can be a life-threatening complication and present with non-specific presentations; thus, it is imperative that it is identified and managed promptly as these cases carry significant morbidity and mortality. Obese patients who undergo bariatric surgery frequently have other co-morbidities; many of which can complicate a case further. Mesenteric vein thrombosis is normally treated with unfractionated or low-molecular-weight heparin. **(Int J Bopmed. 2015;5(3):162-166.)**

Keywords: *mesenteric vein thrombosis; laparoscopic sleeve gastrectomy; obesity; bariatric surgery.*

Introduction

Obesity is a growing problem all over the world, including the United States. The prevalence of obesity continues to rise steadily over the last three decades and is likely to remain on the rise [1]. Bariatric surgery is the most effective treatment of morbid obesity and depending on the type of operation; this *surgery* can also be effective in resolving diabetes [2]. Single-incision laparoscopic sleeve gastrectomy (SILSG) is a surgical procedure for patients who want to lose weight. The operation involves a reduction in stomach size, and the patient is left with a stomach that resembles a tube, which can reduce the sensation of hunger because the part of the stomach that is removed would ordinarily secrete hunger hormones. While the recovery period for such surgeries is often uneventful, one particular case was complicated by the development of a superior mesenteric vein thrombosis, abdominal compartment syndrome and pulmonary emboli. Superior mesenteric vein thrombosis can be a life-threatening complication and can present with non-specific presentations; thus, it is imperative that it is identified as soon as possible and treated immediately.

Literature Search

A PubMed search was performed using the keywords of "sleeve gastrectomy" and "thrombosis". Two other articles in the literature have reported cases similar to this one. "Superior Mesenteric Vein Thrombosis after Laparoscopic Sleeve Gastrectomy" by Pineda postulated that this was induced by a blunt and sharp dissection at the level of the distal stomach, which was close to the pylorus [3].

Bellanger et al. [4] presented three cases of mesenteric

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vein thrombosis development following laparoscopic sleeve gastrectomy. Their practice performed over 800 operations and had three cases of thromboses involving the superior mesenteric vein. Intravenous heparin was started and converted to oral warfarin on discharge for all three cases. No hypercoagulable disorder was discovered in any of the three cases [4].

In addition to the case studies above, D. Goitein et al. [5] performed a retrospective multicenter study and found 17(0.3%) patients out of 5706 who underwent laparoscopic bariatric surgery and had developed portomesenteric vein thrombosis. Patients were treated by anticoagulation with subcutaneous low-molecular-weight heparin (n=15) or intravenous heparin (n=2), followed by warfarin sodium. Three patients were found to have genetic coagulation deficiencies. Management of such cases included rehydration and supportive care, anticoagulation, thrombolysis and if needed, laparoscopy. Acute postoperative portomesenteric vein thrombosis is a rare but life-threatening complication that can occur after SILSG. Early recognition is of paramount importance to prevent the progression into bowel infarction.

This case report is a discussion of the development of superior mesenteric vein thrombosis (SMVT), abdominal compartment syndrome and multiple pulmonary emboli in a patient who underwent SILSG. This location of venous thrombosis can be damaging to other organs and the hypoxic injury from abdominal compartment syndrome resulted in short bowel syndrome. Moreover, this patient developed pulmonary emboli during anticoagulant therapy while in hospital. These were rare occurrences but should be addressed as possible complications for this surgery.

Case Description

A 38-year-old African American female with a body mass index of 48.2 kg/m^2 was admitted for SILSG. The patient's initial physical examination, prior to sleeve gastrectomy, was unremarkable. She was then discharged. However, on readmission several days later, she appeared critically ill. **Her vital signs** were quite unstable. She was pyrexic and tachycardic with a blood pressure hovering around 100/63 mmHg. She was saturating 98% to 100% on 3L of oxygen on nasal cannula. Her abdomen was firm with diminished bowel sounds.

The patient's past medical history included obesity, hypothyroidism, hypertension and dyslipidemia. She was an ex-smoker having quit twenty years ago with one pack year history. Family history was negative.

The patient underwent SILSG and experienced some nausea and vomiting post-operatively, alleviated with antiemetics. She tolerated her bariatric full liquid diet and was discharged home three days later. Subsequently she began to have abdominal pain, nausea and vomiting. A CT scan revealed SMVT with diffuse small bowel ischemia, segmental splenic infarct, main and right portal vein branch thrombosis but no evidence of hepatic ischemia. A thrombectomy was performed by interventional radiology. An exploratory laparotomy demonstrated necrotic bowel due to abdominal compartment syndrome, and 208 cm of small bowel was resected; with a second reexploration and further resection two days later. She had a final abdominal closure whereby the wound was completely closed five days later. She had significant acidosis with pH of 7.19, elevated lactate levels and she required intubation. She was on a heparin drip from the time of diagnosis and underwent bridging for warfarin. She then experienced sudden tachypnea, dyspnea and tachycardia and was found to have multiple pulmonary emboli with pulmonary infarcts on CT pulmonary angiogram. A follow-up CT scan of the abdomen at the end of her hospitalization showed extensive small bowel resection, extensive but stable SMVT, stable splenic infarction, and improved ascites. The patient eventually recovered from her illness and was discharged in a stable condition.

Discussion

SMVT can be a life-threatening complication and present with non-specific presentations; thus it is imperative that it is identified and managed promptly. The mortality rate of acute mesenteric thrombosis can range from 20% to 50% [6]. Presenting symptoms can be mild or severe, and rapid recognition is important. If treated early with anticoagulation and fluids, the progression of the disease can be limited. In addition to developing a mesenteric vein thrombosis, this patient subsequently developed abdominal compartment syndrome which led to short bowel syndrome and pulmonary emboli.

In recent years, laparoscopic sleeve gastrectomy (LSG) has been identified as a newer and innovative approach as a lone-standing surgery for morbid obesity. It is considered easier, faster, and less traumatic to perform for surgeons than laparoscopic Roux-en-Y gastric bypass (LRYGB) [7]. Bariatric surgery is the only evidence based treatment of morbid obesity with proven and sustained weight loss and improvement in comorbidities [8-10]. Initially, LSG was introduced as the first stage in a two-staged bariatric surgical approach but is now accepted as a stand-alone bariatric procedure. It is a desirable procedure comparatively because it reduces the gastric volume while preserving the continuity of the gastrointestinal tract [8]. The sleeve gastrectomy can preserve the integrity of the pylorus and does not include intestinal bypass while the Roux-en-Y does not [2]. In Li's review, the LRYGB group had a higher incidence of complications than the LSG group. The LSG procedure is also safer and less complex than LRYGB and it avoids the long-term sequela of micronutrient deficiency after duodenum exclusion that is seen in the Roux-en-Y procedure [2]. In general, bariatric surgery is successful in reducing the rate of diabetes; although the mechanism for type II diabetes mellitus remission is not particularly clear. V. Vage et al [8] found LSG to have acceptable morbidity-rates and to be an effective procedure overall. It had high resolution rates for diabetes, hypertension, hyperlipidemia, sleep apnea, musculoskeletal pain, snoring, urinary leakage and amenorrhea [8]. There is also an association between LSG and GERD; in Vage's study, the patients who were treated for GERD symptoms preoperatively had resolution of their GERD

symptoms postoperatively [8]. Other improvement shown was that ALT values could also significantly improve after the operation. Obesity associated with non-alcoholic fatty liver disease can also be resolved after bariatric surgery [11]. Some of the advantages include preservation of endoscopic access to the upper gastrointestinal tract, the lack of an intestinal anastomosis thus excluding the risk of internal herniation, normal intestinal absorption and prevention of dumping syndrome due to pylorus preservation [7]. B. Albeladi et al. [7] found that DMII was resolved in 100% of the patients in the LSG vs. 85.7% in the LRYGB group. However, in those where DMII was not resolved, the medication dosage was decreased. Hypertension was resolved in 53.8% of patients with LSG vs. 46.7% with the patients who underwent LRYGB [7]. Having some of these major comorbidities resolve is very favourable for LSG surgery. LSG is also less complex than LRYGB, and leads to a slower operative time as well [7].

Another type of surgery includes laparoscopic adjustable gastric banding surgery (LAGB). This surgery is simple and safe and restricts food by using an adjustable band by creating a pouch that is distended during meals. The banding surgery is similar to the sleeve gastrectomy because they both decrease the volume of the stomach to reduce food intake [12]. The advantages for LAGB include easier technique, shorter operative time, less invasive and fewer early complications. However, a meta-analysis comparing LAGB to LSG has shown that LSG had a better effect on morbid obesity in terms of weight loss and resolution of DMII [12]. Some of the common complications that come with gastric banding include migration of the band (slippage or displacement), band leak, esophageal spasms, and inflammation of the esophagus and GERD.

Reported complication rates for LSG are low, even though the patients undergoing the procedure are of high surgical risk. Major perioperative complications for LSG can include leaks and bleeding. In order to reduce bleeding risks, V. Vage et al. altered their regime for prophylaxis against thrombosis whereby prophylaxis is started post-operatively at a reduced dosage [8]. Some of the complications that can come with doing LSG include hemorrhage, staple line leak, abscess formation, and strictures. The source of the bleeding for hemorrhages can be intraluminal or extraluminal; symptoms include hematemesis or melena stools [13]. Staple line leaks are some of the more serious complications of LSG; and can occur in up to 5% of patients [14]. An early leak is considered one that is diagnosed within the first three days of surgery and a delayed leak is diagnosed more than eight days after surgery [15]. Treatment of the leak usually involves an abdominal washout with surgical repair. Intra-abdominal abscesses can also form as well, and this can be diagnosed with CT scans [13]. Stricture formation can also occur after LSG, presenting either acutely after surgery or later on. These are usually treated with conservative management; however if strictures become chronic, treatment can include endoscopic dilatation [13].

Because deficiencies in micronutrients in morbidly obese patients are frequent, a large number of patients already have nutritional deficiencies prior to bariatric surgery [16]. LSG is a restrictive procedure and lacks the malabsorptive component of LRYGB so the risk for developing deficiencies after surgery is usually considered low. Because of the resection of the fundus, some nutrients like iron or vitamin B12 are less likely to be absorbed [17]. Some patients also develop iron deficiency anemia and this can be explained by LSG. Iron needs to be transformed to an absorbable form by HCl in the normal stomach. The quantity of HCl produced in the stomach is reduced and nutrients can pass the stomach faster after LSG; thus this would be harder to absorb iron [18]. Folate deficiency is also common. Bone metabolism can also change after an LSG but this could also be due to weight loss. This can put them at risk for osteoporosis so this needs to be corrected or treated to avoid deficiency. It is important to supplement the patient after every bariatric procedure to avoid any nutritional deficiency [16]. The etiology for nutritional deficiencies after bariatric surgery is multifactorial but likely due to impaired absorption and decreased oral intake. The most common deficiencies include vitamin B12, vitamin D, folate, iron, and zinc. In general, micronutrient deficiencies were found to be less prevalent after sleeve gastrectomy compared to LRYGB [13]. Routine monitoring is warranted after the surgery so deficiencies can be diagnosed if necessary.

For this patient we chose to anticoagulate with enoxaparin. In a cohort study by Birkmeyer, they evaluated the effectiveness and safety of various different venous thromboembolism prophylaxis strategies for patients undergoing bariatric surgery. They had patients who used unfractionated heparin preoperatively and postoperative, patient who use unfractionated heparin preoperatively and low molecular weight heparin (LMWH) post operatively, and finally a third subset of patients who used low molecular weight heparin both preoperatively and postoperatively [19]. Rates for emboli development were 57% lower for the unfractionated heparin/LMWH group and 66% lower for the LMWH/LMWH group when compared to the unfractionated heparin/unfractionated heparin group[19]. They concluded that low molecular weight heparin was more effective than unfractionated heparin for the prevention of venous thromboembolism and it did not increase the risk of bleeding in bariatric surgery patients. Another study has shown lower rates of bleeding with LMWH compared with unfractionated heparin in general surgery patients [20].

Similar to the other cases found in the literature, this patient was anticoagulated with heparin and bridged to warfarin. There are some suggested etiologies for the cause, including genetic deficiencies (Protein S, Protein C, Antithrombin III, and Factor V Leiden deficiency), prothrombotic states (sepsis, pregnancy, obesity, oral contraceptive use, cirrhosis, lupus anticoagulant, polycythemia vera, heparin-induced thrombocytopenia, and malignancy or myeloproliferative disorders), iatrogenic causes (trauma to the portal venous system, inflammation to the abdominal wall), neoplastic disorders or decreased portal flow [5,6,21]. Venous thromboembolism is a leading cause of mortality after bariatric surgery; the reported frequency of complications involving thromboembolic event in bariatric surgery patients ranges from 0.2% to 2.4%[6]. For this patient, the cause for the multiple thrombi was never discovered.

Mesenteric thromboses have been described as either primary, where no cause is identified, or secondary where there are clear causes and predisposing factors; and 20 to 35% are primary cases [4]. Inappropriate anticoagulant dosing may lead to venous thromboembolism, particularly in obese patients. Frederiksen et al demonstrated that there was a negative correlation with body weight and the anticoagulant effect of a fixed dose of LMWH [22]. Given that the patient did not have a hypercoagulable disorder, it is difficult to determine the reason pulmonary emboli developed. However prolonged immobility, obesity, dehydration and recent surgery could all be seen as risk factors which put this patient in a hypercoagulable state.

The patient in this case study was obese, which increases the risk for hypercoagulability. Obesity is a pro-inflammatory state, and there are higher intra-abdominal pressures in obese patients, which can lead to the formation of venous thrombosis [23]. Studies show that patients who are obese are at a greater risk for thrombosis as well as in patients who are undergoing bariatric surgery, especially for patient with multiple risk factors [24,25]. Some risk factors for venous thromboembolism development include obesity, abdominal surgery, smoking, varicose veins, use of oral contraceptives, history of venous thromboembolism, age greater than 60 years old, and documented venous insufficiency [24]. We chose to anticoagulate using IV heparin with bridging to warfarin, consistent with what other studies have done.

Conclusion

This case study considered a patient who underwent SILSG as surgical management for morbid obesity and subsequently developed SMVT, abdominal compartment syndrome and multiple pulmonary embolisms. While they are rare, these cases carry significant morbidity and mortality, thus requiring immediate attention and treatment. Obese patients who undergo bariatric surgery frequently have other co-morbidities, many of which can complicate a case further. A mesenteric vein thrombosis diagnosis should always be on the differential for abdominal pain, especially if the patient has one or more risk factors. This complication is normally treated with unfractionated or low-molecular-weight heparin.

Competing interests

The authors declare that they have no competing interests.

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