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CONTENTS

ORIGINAL ARTICLES

Cardiology

- Dynamic Networks of Human Homeostatic Control in Norm (Part 1)**
A. Kruglov, G. Gebel, V. Utkin, A. Vasiliev, V. Sherman 101

Obstetrics and Gynecology

- Receiver-Operating Characteristic Analysis for Evaluating the Severity of the Condition of Preterm Children Depending on Perinatal Risk Factors, Timing, and Mode of Delivery**
A. Orazmuradov, S. Konnon, N. Zakharova, A. Lukaev 106

Urology

- The Immediate Results of Surgical Treatment of Bladder Cancer**
A. Charyshkin, D. Matorkin, V. Demin 110

Abdominal Surgery

- Preperitoneal Blockade in the Treatment of Patients with Perforated Gastroduodenal Ulcers and Peritonitis**
A. Charyshkin, S. Yakovlev, V. Demin 114

Psychiatry

- Combined Antirelapse Therapy in Patients with Schizoaffective Disorder: A Prospective Cohort Study**
M. Nekrasov, D. Khritinin, M. Sumarokova, Zh. Gardanova, et al. 119

Ophthalmology

- Effectiveness of Photodynamic Therapy in the Healing of Corneal Alkali Burn in Rats**
F. Bakhrtdinova, K. Narzikulova, S. Mirrakhimova, Akshay Khera 124

CONTENTS

CONTINUED

REVIEW & CASE REPORT

- Association of Chronic HBV Infection with Chronic Lymphoproliferative Disorders:
A Review and Case Report**
S. Sleptsova, V. Yadrichinskaya, A. Palchina, N. Borisova, et al. 128

SHORT COMMUNICATION

- Reproductive Function in Patients with Non-functioning Pituitary Adenoma According
to the Register of the Republic of Uzbekistan**
Z. Halimova, D. Kholova, Yu, Urmanova, D. Alieva, et al. 133
- Antioxidant Bio-Complexes from Renewable Arctic Raw Materials**
A. Stepanova¹, V. Anshakova, Ya. Slepokurov, A. Zagorenko, et al. 136

CURRENT CONCEPTS

- How Health Relationship Management Services (HRMS) Benefits the Elderly**
Cynthia Meckl-Sloan 138
- How Health Relationship Management Services (HRMS) Benefits Corporate Wellness**
Nik Tehrani 143
- How Health Relationship Management Services (HRMS) Benefits Telemedicine**
Nik Tehrani 146

READER SERVICES

- Instructions for Authors** 149

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Dynamic Networks of Human Homeostatic Control in Norm (Part 1)

Alexander G. Kruglov, PhD, ScD; Georgiy Y. Gebel†, PhD, ScD; Valery N. Utkin;
Alexander Yu. Vasiliev, PhD, ScD; Veronoca A. Sherman

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Abstract

The research has been undertaken to study the regional and common relationships between hemodynamic and metabolic parameters of human body functioning in individuals without clinical signs of pathology (in “norm”). Indicators of hemodynamics and metabolism were obtained by catheterization in a variety of areas: LV, RV, RA, CS, Ao, fixed SS, IJV, SVC, RHV, renal vena, and PT. Correlation and factor analyses were conducted for the study of: 1) the relationship between biochemical parameters in the blood stream, 2) the relationship between hemodynamic parameters, 3) relationship between the hemodynamic and biochemical parameters. Due to the nature of the correlation analysis, the significant ($p < 0.05$) relation signs (+, 0, -) without regard to their power were considered. The obtained results in the study of brain blood flow, heart, liver, lungs, kidneys suggested the existence of the primary homeostatic control of the factors determining rheological and thrombogenic properties of blood; the regulation of brain gas exchange and intracranial venous pressure by the minimum level of pressure in the cerebral outflow pathway—the pressure in RA; the regulating relationships between blood flow in CS with blood flow in RHV, RA, SS, and LV; and the existence of a synergistic complex of the relationships between the studied biochemical and hemodynamic characteristics that form the human homeostasis control matrix in norm. (*Int J Biomed.* 2016;6(2):101-105.)

Key Words: human homeostasis control matrix • hydrodynamic balance • hepatic venous outflow • coronary sinus

Abbreviations

Ao, aorta; **AVDO₂**, arterio-venous oxygen content difference; **BP**, blood pressure; **BSBR**, basic set of biochemical regulations (constant during one cardiac cycle); **CO**, cardiac output; **CS**, coronary sinus; **DP**, diastolic pressure; **Er**, erythrocyte; **EDP**, end-diastolic pressure; **F-n**, fibrinogen; **IJV**, internal jugular vein; **IVC**, inferior vena cava; **LV**, left ventricle; **LA**, left atrium; **M**, maximum pressure; **MP**, medium pressure; **N**, Norm; **P-n**, total protein; **PI**, plasma; **PP**, pulse pressure; **PT**, pulmonary trunk; **RA**, right atrium; **RV**, right ventricle; **RHV**, right hepatic vein; **SS**, sigmoid sinus; **SinP**, sigmoid sinus pressure; **SVC**, superior vena cava; **SP**, systolic pressure; **SVP**, hepatic sinusoidal pressure; **SAH**, stable arterial hypertension; **SV**, stroke volume.

Introduction

The objective of the research was to identify the local and interregional qualitative relationships between indicators of blood chemistry; intraorgan and interregional hemodynamic correlations; the relationships between biochemical and hemodynamic parameters; the role of RA in the regulation of inter-organ relationships. For our research purposes, we opted

for the hemodynamic pathway: LV—SS—IJV—SVC—RA.

The results of these studies—as well as data of biochemical status, the levels of sinusoidal venous pressure of RHV and CS, obtained during catheterization in the group of healthy people (the norm)—have been repeatedly published previously.^[1-4] We estimated the gradients of venous drainage from the liver; relationships between hemodynamic parameters and biochemical parameters of CS.

The aim of the study was also to supplement the matrix of interregional interrelations^[5] of studied parameters with data of the relationships between the hemodynamic parameters of RHV and CS.

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Materials and Methods

All of the research through which we received the discussed results was conducted in the same laboratory and with the help of the same methods in the supine position (in the perpendicular position to the vector of gravity when its influence in all parts of the venous system is equal). The data obtained by using the catheterization performed with a probe show BP levels and biochemical parameters at the outflow from the organ (brain and liver).

We performed the catheterization of LV, Ao, IJV, SVC, RHV, IVC, RA, RV, PT, and renal vein;^[5-11] during the procedure the pressure levels were recorded and blood samples were collected. The catheterization was performed by percutaneous puncture of the right femoral artery and the right femoral vein under local anesthesia, using the Seldinger technique. A vein dilator was used during the vein puncture. The catheter reached the aforesaid parts of the cardiovascular system. The arterial pressure values were recorded for the thoracic aorta. The studies were monitored by using radiography equipment.

The results for assessment were obtained from the studies conducted on apparently healthy people who were thoroughly examined in hospital before complex reconstructive maxillofacial surgery (these data have been represented in our early research papers). The total number of the examined people was 60 (48 men and 12 women). The age of 52 of those people ranged from 20 to 45, and 8 people were over 45 years old. In 18 (13 males and 5 females aged from 21 to 42 years) people, out of necessity, catheterization of CS (for estimation of biochemical and hemodynamic parameters in 6 persons) and RHV (for biochemical parameters in 11 people and hemodynamic parameters in 14 people) was conducted. Statistical analysis was performed using the statistical software «Statistica 12.0».

Results and Discussion

When assessing the results, we took into consideration some principles of the general system theory, namely, regulation theory. Maintaining a constant internal environment when external conditions change is formulated as a homeostatic regulation. If there is a multitude of functional stability parameters, the self-regulating homeostatic system will find this multitude and restore the stability of the system, regardless of any changes in the environment.

The range of physiological changes, within which the optimum life activity for the present environment persists, is seen as normal. To define boundaries of the normal range we used the confidence interval boundaries set for each parameter and value; these boundaries define the range within which the probability of the relevant parameter value is 95%. We have investigated the values of the following parameters: content levels of plasma electrolytes (K, Na) and red blood cells (Er); blood gases (pO₂, pCO₂); acid-base composition (pH, SB); blood proteins: hemoglobin (Hb), F-n, total protein (P-n); and arterial venous difference (AVDO₂) in some segments.

We have investigated the following parameters of

central and systemic hemodynamics (expressed in mmHg): M, DP, PP, MP, F.d.p. for left and right ventricles, and A/ X/ V/Y waves for RA.

The correlation analysis was conducted to study the relationship between the biochemical characteristics of the blood flow and the hemodynamic values of the cerebral blood inflow and outflow in apparently healthy people and to compare them with the respective characteristics of the SAH group.^[12]

The comparison of the sets of correlation relationships between biochemical and hemodynamic parameters revealed a drastic change in the entire set of relationships typical of norm, including loss of correlations with the end products of brain metabolism (pO₂, the pCO₂, etc.) and between parameters of cerebral flow and rheology, which describe the general and plasma viscosity (Hb, F-n) in the cerebral outflow pathway. Normally, the hydrodynamic pressure in SS varies in accordance with changes in oncotic and gas pressure, as well as blood viscosity parameters. These connections are lost in SAH.

The results obtained and processed by methods of mathematical statistics and presented in^[4] and a number of our works suggest that rheological properties of blood (its viscosity) can be seen as an initially regulated parameter of homeostasis. We assume, as proven, that the integrated hydrodynamic formation (SS-IJV-SVC-RA—is one of the cerebral gas exchange regulators, where the main regulator is the minimum pressure along the pathway of cerebral blood outflow - pressure in RA.

Earlier, we have discussed the results of our research,^[3,12-18] which allow us to review and analyze cardiac hemodynamics as a “single entity” consisting of functional units: 1) “atrial unit” - RA and LA; 2) “aorto-pulmonary unit” - bulb of the aorta and PT; 3) “three-chamber unit” of ventricles, consisting of a) “the left chamber” (LV) and b) “the right chamber” (RV) with blood outflow from the chambers into “aorto-pulmonary unit”, and c) “spongy” venous chamber with blood outflow from the myocardium (during the united systole) through CS and Thebesian veins into the “atrial unit.” During “united systole” of “three-chamber unit” of ventricles, the following blood volumes are moved: 1) LV and RV stroke volume into the “aorto-pulmonary unit”; 2) stroke volume from the “spongy” venous chamber into the “atrial unit” (volumes of #1 and #2 constitute a united stroke volume of the “three-chamber unit”; and 3) blood inflow from SVC/IVC and pulmonary veins into the “atrial unit” during systolic/membrane blood suction and during the retraction of the tricuspid and mitral valves in the ventricular cavity during the blood expulsion from them. Thus, a united systole of “three-chamber unit” of ventricles is the basis for regulation: 1) the inflow (mobilization) of blood into the “atrial unit”; 2) systolic synchronization of hemodynamics in the “aorto-pulmonary” and “atrial” units; 3) intracardiac conditions of blood outflow from all chambers of the “three-chamber unit” of the ventricles through the fixed rings of CS, truncus pulmonalis, and bulb of the aorta. The volume of the blood moved by ventricular myocardium during this period is more than a united stroke volume by the amount of venous blood mobilized to the “atrial unit.”

X-collapses in RA create a stable phase gradient of the venous drainage from the liver into RA.^[2,19] It remains positive (i.e., provides a constant outflow from RHV into RA) throughout the united systole of the “ventricular unit,” when the other phase gradients are zero or negative.^[2,19] It was shown that there is a synchronization of this flow with the same phases of flow outflow from the brain, lungs, and kidneys. As manifestations of a single process (myocardial contractility), all the indicators of a period of united systole change conjugate. We believe that this is the basis of the systolic regulation of venous outflow from the organs (including the liver) into the “atrial unit.”

A phase of the diastolic synchronization of intraorgan pressures, which takes place on the background of end-diastolic pressures in the ventricles, aorta, and pulmonary artery, occurs at open atrio-ventricular valves and the created united chambers: 1) “RV, RA, the veins of the great circle”; 2) “LV, LA, pulmonary veins.” In this phase, there is a minimization of the differences between the levels and gradients of the pressures inside of the united chambers and between them. Our data [1] allow to consider CS not only as a vessel for venous blood flow from the myocardium, but also as a channel of intracardiac regulation of LV function by the level of booster pressure in RA, and by the level of pressure in the united chamber (RV-RA) in phase of diastolic synchronization.

During united systole of the “ventricular unit,” an impulse of pulse wave reaches all segments of the arterial system until the closure of the aortic valve, in the period of maximum pressure of united hemodynamic chamber - (LV-aorta). The spherical dissipative wave structure of pulse flow provides the most energy and information-rich processes of the aortic chamber, being one of the foundations of the urgent regulation, an adaptation. Thus, the heart moves not only the hemodynamic volumes in the vascular bed, but also generates the control-wave signals spreading to the exchange zones of organs. A general and regional vascular resistance with reduced vascular resistance in areas of increased metabolism (increased blood flow) is a mosaic information field for the source of the laminar arterial pressure (heart).

The obtained hemodynamic parameters of right HV, PT and CS allow us to group the extended summary matrix table (Table 1) of synergistic relationships for parameters of metabolism and hemodynamics in addition to the human homeostasis control matrix in norm published earlier.^[5]

Conclusion

Our findings suggest that the dynamic processes of RA hemodynamics are a zone of unstable hydrodynamic balance within from 0 to 10 mmHg, having a number of fixed values (equal to pressure levels in pressure-bearing veins) synchronized with the phases of evolution of the cardiac cycle, which are the derived values from the dynamics of the cardiac cycle, as well as the threshold values for wave-control signals spreading to the exchange zone of organs, including the human heart.

The united systole of the “ventricular unit,” in

conjunction with the diastolic evolution of displacement of venous blood volumes of the right parts of heart, creating a wave pulses throughout the vascular system, provides to the heart the complete information volume of the common and regional mosaic vascular resistance, depending on the local metabolic activity during one cardiac cycle. We believe it is possible to assert that the generation of described wave processes by a united systole of the “ventricular unit” during one cardiac cycle in the arterial and venous flow creates a uniform pattern of control signals for the exchange areas of human organs, as well as information feedback signals for the “unified heart,” affecting the structure of the next cardiac cycle.

Competing interests

The authors declare that they have no competing interests.

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Table 1.

The extended summary matrix table of synergistic relationships for parameters of metabolism and hemodynamics

		Ao				RA				RV			LV		CO	SV	SinP				BSBR								
		SP	DP	PP	MP	A	X	V	Y	MP	EDP	MP	SP	PP			SP	DP	PP	MP	K er	Ht	F-n	P-n	H-b				
Ao	K pl					-	-	-	-	X	X	X	X	X	X	X	+												-
	K er									X	X	X	X	X	X	X	-	-	-										
	Na pl							-	-	X	X	X	X	X	X	X	+	+							-	-	-	+	
	Na er					-	-	-	-	X	X	X	X	X	X	X	-								+				
	pH							+	+	X	X	X	X	X	X	X	-	-	-								+	-	+
	pCO ₂		-		-					X	X	X	X	X	X	X													
	SB		-		-					X	X	X	X	X	X	X	-	-	-										
	pO ₂				+					X	X	X	X	X	X	X	+	+		+	+						-	+	
	HbO ₂							+		+	X	X	X	X	X	X													-
	Hb								+	X	X	X	X	X	X	X	-	-	-						+	+	-		
	Ht					+	+	+	+	X	X	X	X	X	X	X	-	-	-								+	+	+
	F-n	+	+			-	+			X	X	X	X	X	X	X	-	-	-						+		+	+	
	P-n									X	X	X	X	X	X	X	+	+		+							+		-
SinP	K pl					-	-	-	-	X	X	X	X	X	X	-	-	-								+			
	K er						-	+	+	X	X	X	X	X	X														
	Na pl		+		+			-	-	X	X	X	X	X	X	+	+		+	+	+						+		
	Na er									X	X	X	X	X	X									+					
	pH					-		+	+	X	X	X	X	X	X	-	-	-						-	-	+			
	pCO ₂									X	X	X	X	X	X		+												
	SB							+		X	X	X	X	X	X	-	-	-								+			
	pO ₂							-	-	X	X	X	X	X	X									+					
	HbO ₂					-	-	-	-	X	X	X	X	X	X													-	
	Hb							-		X	X	X	X	X	X	-	-	-											
	Ht						+	+	+	X	X	X	X	X	X												+		
	F-n		+	-		-	-	+	-	X	X	X	X	X	X	-	-	-									-		
	P-n									X	X	X	X	X	X	+			+							-			
ABDO ₂	X	X	X	X	+	-	+	+	X	X	X	X	X	X	X		+		+	-						+	+		
SinP	SP				+	-	+			+		+	-	-	-		X	X	X	X									
	DP		+		+		+			+		+	-	-	-		X	x	X	X									
	PP		-				-			+							X	X	X	X									
	MP				+		+		+	+	-	+	-	-	-		X	X	X	X					X	X	X	X	
SVP	SP		-	+	-	-	-	-	-	-	-	+	X	X	X	X	-	-	-	-									
	DP		-	+	-	-	-	-	-	-	-	+	X	X	X	X	-	-	-	-									
	PP							-	-		+	+	X	X	X	X	-	-	-	-									
	MP		-	+	-	-	-	-	-	-	-	+	X	X	X	X	-	-	-	-									
PT	SP	+	+		+	+	+	+	+	+	+		X	X	X	X	+	+		+									
	DP		+		+					+			X	X	X	X			-										
	PP	+			+	+				+			X	X	X	X	+	+	+	+									
	MP	+	+		+	+	+	+	+	+	+	+	X	X	X	X		+	-										
CS	SP	+	+	-	+	+	+	+	+	+	+	-	X	X	X	X	+	+	-	+									
	DP		+	-	+	+	+	+	+	+	+	-	X	X	X	X	-	-	+	-									
	PP		+	-					+			-	X	X	X	X	+	+	-	+									
	MP	+	+	-	+	+	+	+	+	+	+	-	X	X	X	X	-	-	+	-									

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Receiver-Operating Characteristic Analysis for Evaluating the Severity of the Condition of Preterm Children Depending on Perinatal Risk Factors, Timing, and Mode of Delivery

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Abstract

The aim of this study was to assess the role of the receiver-operating characteristic (ROC) analysis for evaluating the severity of the condition of preterm children, depending on perinatal risk (PR) factors, timing, and mode of delivery.

In order to identify the thresholds for "intrapartum gain" of risk factors for timely selection of mode of delivery, we performed a comparative ROC analysis of the severity of the state of children at birth according to the Apgar score, from 1 point in the first minute to 7 points in the fifth minute of life. The analysis of indicators of perinatal mortality (PM) and perinatal morbidity (Pmb) shows a statistically significant difference ($P < 0.05$) in the selection of the priority mode of delivery for women with premature birth during all analyzed gestation ages, depending on PR: frequency of PM and Pmb is lower among pregnant women with a high risk who gave birth to premature babies delivered by C-section. (*Int J Biomed.* 2016;6(2):106-109.).

Key Words: perinatal mortality • perinatal morbidity • preterm delivery • ROC analysis • perinatal risk factors

Introduction

Premature birth (PB) is one of the most important problems in maternal and child health, as such births directly influence perinatal morbidity (Pmb) and perinatal mortality (PM). Around the world, somatic illness, implementation of the assisted reproductive technologies (ART) and the rise in the number of multiple births have led to an increased frequency of PB. The highest percentage of preterm delivery occurs between 34 and 37 weeks of gestation, while this percentage is 12 times less in the gestational period between 22 and 27 weeks.^[1]

Infant mortality and child morbidity has been significantly reduced worldwide in the past 30 years. This is due to progress in the special care for premature infants. This trend is especially typical of developed countries. In the USA, the frequency of PB rose from 9.4% to 12.8% due to an increase in the number of multiple births on the background of ART in past 25 years.^[2,3]

The outcome of PB for the newborn depends on several factors: gestational age, presence of extragenital complications,

the severity and nature of complications of pregnancy, and the type of fetal presentation.^[4]

The aim of this study was to assess the role of the receiver-operating characteristic (ROC) analysis for evaluating the severity of the condition of preterm children, depending on perinatal risk (PR) factors, timing, and mode of delivery.

Materials and Methods

The study was carried out in CMH № 29 named after N.E. Bauman. We carried out a prospective analysis of 236 medical records of pregnant women at 28 to 33 weeks (plus 6 days) of gestation. According to PB classification, all pregnant women were divided into 2 cohorts: Cohort 1 (gestational age from 28 to 30 weeks plus 6 days) and Cohort 2 (gestational age from 31 to 33 weeks plus 6 days). At admission, every patient was evaluated for PR factors. Depending on the amount of PR factors, each cohort was divided into 3 groups: Group 1 (low risk), Group 2 (moderate risk), and Group 3 (high risk).

We identified the degree of PR based on the scale developed by O. G. Frolova and E. I. Nikolaeva (1981) and modified by V. E. Radzinsky et al.^[5] The scale includes a number of parameters divided into blocks: socio-biological block, data of obstetric and gynecological history, extragenital diseases of mother, complications of pregnancy, and fetal

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assessment. A specific group for PR was defined in accordance with the number of points derived from S. Knyazev's scale (2003). Low risk (<15 points), moderate risk (from 15 to 20 points), and high risk (>25 points). Calculation of PR factors was performed twice: at admission and during labor. The ratio of these indexes determines the so-called "intrapartum gain" (IG) of PR factors.

Statistical analysis was performed using the SPSS for Windows. Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean (M) and standard error of the mean (SEM) for continuous variables. Group comparisons with respect to categorical variables are performed using chi-square test. A probability value of $P < 0.05$ was considered statistically significant. ROC analysis was performed using MedCalc.

Results and Discussion

At admission to the maternity hospital, all pregnant women underwent tocolytic therapy, including intrapartum tocolysis or treatment with magnesium sulfate.

Vaginal birth occurred in 65.3% of surveyed women, and Cesarean delivery was performed in 34.7%. Evaluation of indications for abdominal delivery in pregnant women with preterm pregnancy showed that 19.5% had a low PR, 39.0% had a moderate PR, and 41.5% a high PR. The main indications for operative delivery were the progression of gestational toxicosis (22%), abnormal fetal position (22%), and acute hypoxia (18.3%).

In order to identify the thresholds for IG of risk factors for timely selection of mode of delivery, we performed a comparative ROC analysis of the severity of the state of children at birth according to the Apgar score (AS),^[6,7] from 1 point in the first minute to 7 points in the fifth minute of life (Table 1).

Table 1.
Number of newborns with AS from 1 to 7 points

Cohort	Degree of PR	n	Newborns with an AS of 1 point on the 1st minute to 7 points on the 5th minute of life		Number of deaths	
			n	%	n	%
I	low	20	4	20,0	1	5,0
	moderate	38	12	31,6	4	10,5
	high	70	24	34,3	1	1,4
II	low	32	13	40,6	0	0,0
	moderate	52	17	32,7	1	1,9
	high	24	8	33,3	1	4,2
Summarized						
Degree of PR	Total	Newborns with an AS of 1 point on the 1st minute to 7 points on the 5th minute of life		Number of deaths		
		n	%	n	%	
low	52	17	32.7	1	1.9	
moderate	90	29	32.2	5	5.6	
high	94	32	34.0	2	2.1	

Note: No statistically significant differences ($P > 0.05$).

The prognostic value of IG for risk factors for PMb and PM was obtained by assessing the area under the curve (AUC): 0.9–1.0, excellent; 0.8–0.9, very good; 0.7–0.8, good; 0.6–0.7, tolerable; and <0.6, deficient.^[8,9]

1. For pregnant women with a low PR, AUC was 0.821 ± 0.062 and the studied model could be evaluated as very good, which predicted a probability of childbirth with a low AS due to a high level of PMb, depending on the increase in points. The cut-off level was an IG of 51.5% with diagnostic sensitivity of 82.4% and specificity of 88.6%. The total number of newborns with an AS of 1 to 7 points was 52, including 17 with a low AS. Under the threshold of 51.5%, we identified 34 newborns, including 3 newborns with a low AS. Among 18 newborns from mothers with an IG more than 51.5%, 14 had a low AS (Figure 1, Tables 2 and 3).

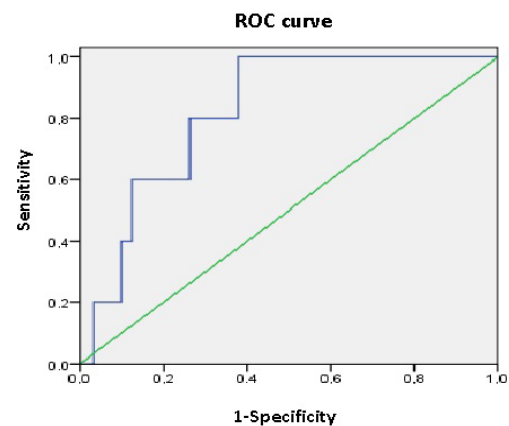


Fig. 1. ROC curve for AS and IG (51.5%)

Table 2.
Prognostic value of IG for risk factors for PMb and PM

Test Results		Number of newborns with an AS of 1 to 3 points	Number of newborns with an AS of 4 to 7 points
IG	>51.5%	14	4
	<51.5%	3	31

sensitivity	82.4%
specificity	88.6%
accuracy	86.5%

Table 3.
Area under the curve

Area	Standard error	Asymptotic significance	Asymptotic 95% CI	
			lower limit	upper limit
.821	.062	.015	.700	.942

2. For pregnant women with a moderate PR, AUC was $0,754 \pm 0,063$ and the studied model could be evaluated as good, which predicted a probability of childbirth with a low AS due to a high level of PMb, depending on the increase in points. The cut-off level was an IG of 39.5%. The total number of newborns with an AS of 1 to 7 points was 90, including 29 with severe asphyxia. Under the threshold of 39.5%, we identified 27 newborns, including 23 newborns with severe asphyxia (Figure 2, Tables 4 and 5).

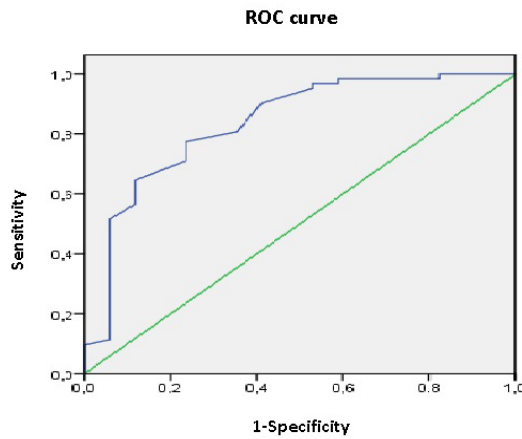


Fig. 2. ROC curve for AS and IG (39.5%)

Table 4.

Prognostic value of IG for risk factors for PMb and PM

Test Results		Number of newborns with an AS of 1 to 3 points	Number of newborns with an AS of 4 to 7 points
IG	>39.5%	23	4
	<39.5%	6	31

sensitivity	79.3%
specificity	88.6%
accuracy	84.4%

Table 5.

Area under the curve

Area	Standard error	Asymptotic significance	Asymptotic 95% CI	
			lower limit	upper limit
.754	.063	.001	.630	.877

3. For pregnant women with a high PR, AUC was $0,889 \pm 0,052$ and the studied model could be evaluated as very good, which predicted a probability of childbirth with a serious condition, depending on the increase in points. The cut-off level was an IG of 30.5%. The total number of newborns with

an AS of 1 to 7 points was 94, including 32 newborns with a low AS. Under threshold less of 30.0%, we defined 35 newborns, including 24 newborns with a low AS (Figure 3, Tables 6 and 7).

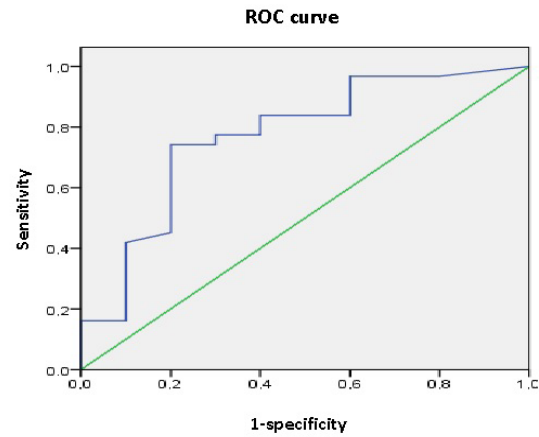


Fig. 3. ROC curve for AS and IG (30.0%)

Table 6.

Prognostic value of IG for risk factors for PMb and PM

Test Results		Number of newborns with an AS of 1 to 3 points	Number of newborns with an AS of 4 to 7 points
IG	>30.0%	8	51
	<30.0%	24	11

sensitivity	75.0%
specificity	82.3%
accuracy	79.8%

Table 7.

Area under the curve

Area	Standard error	Asymptotic significance	Asymptotic 95% CI	
			lower limit	upper limit
.889	.052	.000	.787	.991

Thus, the predicted relative risk of delivering a child with a low AS and a predictable PM among women with a low PR corresponds to IG >51.5% (RR=3.20, 95% CI:3.20-1.75) (Table 8). The predicted relative risk of delivering a child with a low AS and a predictable PM among women with a moderate PR corresponds to IG >39.5% (RR=5.38, 95% CI:2.86-10.11) (Table 9). The predicted relative risk of delivering a child with a low AS and a predictable PM among women with a high PR corresponds to IG >30% (RR=4.23, 95% CI:2.39-7.49) (Table 10).

Table 8.

Predicted relative risk of delivering a child with a low AS and a predictable PM among women with a low PR

IG	AS of 1 to 3 points		AS of 4 to 7 points		P
	n	%	n	%	
> 51.5%	14	77.8	4	22.2	<0.001
<51.5%	3	8.8	31	91.2	<0.001

Table 9.

Predicted relative risk of delivering a child with a low AS and a predictable PM among women with a moderate PR

IG	AS of 1 to 3 points		AS of 4 to 7 points		P
	n	%	n	%	
> 39.5%	6	9.5	57	90.5	<0.001
<39.5%	23	85.2	4	14.8	<0.001

Table 10.

Predicted relative risk of delivering a child with a low AS and a predictable PM among women with a high PR

IG	AS of 1 to 3 points		AS of 4 to 7 points		P
	n	%	n	%	
> 30.0%	8	13.6	51	86.4	<0.001
<30.0%	24	68.6	11	31.4	<0.01

Conclusion

Thus, the analysis of indicators of PM and PMb shows a statistically significant difference ($P < 0.05$) in the selection of the priority mode of delivery for women with premature birth during all analyzed gestation ages, depending on PR:

frequency of PM and PMb is lower among pregnant women with a high risk who gave birth to premature babies delivered by C-section. A C-section for preterm labor at the gestational age of 28-33 weeks (+6 days) should be considered if IG is:

- > 50% (RR=3.20, 95% CI:3.20-1.75) for a low PR
- > 40% (RR=5.38, 95% CI:2.86-10.11) for a moderate PR
- > 30% (RR=4.23, 95% CI:2.39-7.49) for a high PR.

Competing interests

The authors declare that they have no competing interests.

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The Immediate Results of Surgical Treatment of Bladder Cancer

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Abstract

The objective of this study was to evaluate the immediate results of the use of ureterointestinal anastomosis according to the Bricker technique at radical cystectomy (RC) for bladder cancer (BC).

Materials and Results: The study included 96 patients (11.5% women and 88.5% men) with BC, aged from 31 to 74 years (mean age 63.8±7.2), who underwent RC in the Lipetsk Regional Oncology Center, in the period from 2005 to 2014.

Among the early postoperative complications, we identified dynamic ileus (16.7%), inflammatory complications of the surgical wound (12.5%), acute pyelonephritis (10.4%), and failure of ureterointestinal anastomosis (4.2%). The frequency of postoperative acute pyelonephritis corresponded to the findings of other authors. Two (2.1%) patients died from early postoperative complications because of concomitant diseases (ischemic heart disease, myocardial infarction); thus, postoperative mortality in the early postoperative period was 4.2%. Chronic pyelonephritis with chronic renal failure detected in 15(15.6%) patients after one year after surgery was the most frequent late postoperative complication. The stricture of ureterointestinal anastomosis in 9(9.4%) patients has been eliminated through relaparotomy and resection of anastomosis. The development of urolithiasis in 12(12.5%) patients after one year after surgery has required the implementation of contact lithotripsy and litholytic therapy. (**Int J Biomed.** 2016;6(2):110-113.)

Key Words: bladder cancer • radical cystectomy • ureterointestinal anastomosis • postoperative complications

Introduction

Currently, malignant neoplasm of the bladder is a frequent urinary tract malignancy. In the entire structure of cancer pathology in Russia, bladder cancer is diagnosed in 4.5% of men and 1% of women.^[1-3] Mortality in patients with BC in Russia remains high and exceeds global mortality by 19.8%.^[1-3] In 45% of patients, BC is found in the early stages. The annual global BC incidence reached up to 335.8 thousand people.^[2-8] Malignant transformation of the urothelium occurs at disturbances of molecular interactions that regulate cellular homeostasis.^[1,2,9-12] One of the main risk factors for bladder cancer is a genetic predisposition.^[1,2,13,14] A number of studies have identified numerous genetic changes, which, directly or indirectly, contribute to the formation of bladder tumors.^[1-3,15-17]

In modern oncology, radical cystectomy is the standard treatment for muscle invasive bladder cancer.^[1-3,16] According to statistics, 57% of patients who underwent RC had a primary muscle invasion.^[1-3] About 30% of patients with muscle invasive bladder cancer at the time of disease detection have undiagnosed distant metastases, and 25% of patients receive radical surgical treatment at already existing lesions of the lymph nodes.^[13,14,18]

Radical cystectomy involves complete removal of the bladder with lymph node dissection. Pelvic lymphadenectomy can reduce the risk of local recurrence and potentially improve a cancer-specific survival. According to the literature, an extended pelvic lymphadenectomy has a prognostic advantage compared to the standard lymphadenectomy for bladder cancer.^[1-5,16]

Radical cystectomy is one of the most traumatic operations, so that the risk of early and late postoperative complications is high.^[1-3,18] Choosing the best treatment options for patients with this pathology still remains one of the most complex and controversial issues among the various surgical schools and directions.

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The main objective of our study was to evaluate the immediate results of the use of ureterointestinal anastomosis according to the Bricker technique at radical cystectomy for bladder cancer.

Materials and Methods

The study was retrospective, controlled, and non-randomized. The number of patients for primary selection was 706; the number of patients included in the subsequent analysis was 96. Inclusion criteria were age 31 years and older, male and female, stage I-III muscle-invasive bladder cancer, a radical cystectomy. Exclusion criteria were myocardial infarction and acute cerebrovascular accident.

All 96 patients (11.5% women and 88.5% men) with bladder cancer, aged from 31 to 74 years (mean age 63.8 ± 7.2), underwent radical cystectomy in the Lipetsk Regional Oncology Center, in the period from 2005 to 2014. Baseline demographic characteristics of patients enrolled in this study are presented in Table 1.

All patients were examined according to treatment-diagnostic standards. This examination included general clinical, laboratory and special instrumental investigations (X-ray, endoscopy, ultrasound, histological research methods). If necessary, we perform echocardiography, ultrasound examination of abdominal cavity and retroperitoneal space.

Table 1.

Baseline demographic characteristics of patients

Age (y)	Gender		Number of patients
	Male	Female	
31–40	2 (2.1 %)	-	2 (2.1%)
41 - 50	7 (7.3 %)	2 (2.1 %)	9 (9.4%)
51 - 60	28 (29.1 %)	4 (4.2 %)	32 (33.3%)
61 - 70	29 (30.2 %)	4 (4.2 %)	33 (34.4%)
≥71	19 (19.8 %)	1 (1.0 %)	20 (20.8%)
Total	85 (88.5 %)	11 (11.5 %)	96 (100%)

Ureterointestinal anastomosis was performed according to the Bricker technique: The urethras were crossed in their lower third and intubated with corresponding diameter drains. A mobilization of ileum site with a length of 30 cm to 40 cm was performed. The integrity of the intestinal tract was restored by anastomosis between the proximal and distal ends of the intestine. A single-row anastomosis was imposed between the urethra distal end and the intestine wall — “end-to-side.” A urostomy was formed in the abdominal wall.

Evaluation of the functional condition of the kidneys and urinary tract in the early and late postoperative periods was carried out on the basis of a comprehensive examination, including the assessment of the level of serum creatinine, electrolytes, acid-base balance of blood, ultrasonography of the upper and lower urinary tract, excretory urography, reoscintigraphy, retrograde and antegrade pyelography with the Whitaker test, computed tomography of the abdomen and pelvis, complex urodynamic study and cysto- and ureteroscopy

if it is required.

The study was conducted in accordance with ethical principles of the Declaration of Helsinki. It was approved by the by Ethics Committee at the Lipetsk Regional Oncology Center. Written informed consent was obtained from all participants. Statistical analysis was performed using the statistical software «Statistica». (v6.0, StatSoft, USA).

Results and Discussion

Among the early postoperative complications, we identified dynamic ileus (16.7%), inflammatory complications of the surgical wound (12.5%), acute pyelonephritis (10.4%), and failure of ureterointestinal anastomosis (4.2%). It should be noted that the dynamic ileus was the most common complication among the early postoperative complications (Table 2). The treatment of this complication included installation of a nasogastric tube to evacuate the stomach contents, prolonged epidural anesthesia, bowel stimulation, cleansing enemas, and infusion therapy. The failure of ureterointestinal anastomosis was found in 4(4.2%) patients; in these cases we conducted relaparotomy, sanitation, and drainage of the abdominal cavity, and then after closing, anastomotic defect drains were removed.

Table 2.

Early postoperative complications in patients with bladder cancer (n=96) in the period from 2005 to 2014

Early postoperative complications	Number of patients
Dynamic ileus	16 (16.7 %)
Inflammatory complications of the surgical wound	12 (12.5 %)
Acute pyelonephritis	10 (10.4%)
Failure of ureterointestinal anastomosis	4 (4.2%)
Total	42 (43.8 %)

The frequency of postoperative acute pyelonephritis corresponded to the findings of other authors. Two 2(2.1%) patients died from early postoperative complications because of concomitant diseases (ischemic heart disease, myocardial infarction); thus, postoperative mortality in the early postoperative period was 4.2%.

Among late postoperative complications (Table 3), we identified chronic pyelonephritis with chronic renal failure (15.6%), urolithiasis (12.5%), and a stricture of ureterointestinal anastomosis (9.4%).

The average life expectancy of patients with bladder cancer on whom we operated was 786 ± 150.5 days. Chronic pyelonephritis with chronic renal failure detected in 15(15.6%) patients after one year after surgery was the most frequent late postoperative complication. The stricture of ureterointestinal anastomosis in 9(9.4%) patients has been eliminated through relaparotomy and resection of anastomosis. The development of urolithiasis in 12(12.5%) patients after one year after surgery has required the implementation of contact lithotripsy and litholytic therapy.

Table 3.

Late postoperative complications in patients with bladder cancer (n=96) in the period from 2005 to 2014

Late postoperative complications	Number of patients
Chronic pyelonephritis with chronic renal failure	15 (15.6 %)
Urolithiasis	12 (12.5 %)
Stricture of ureterointestinal anastomosis	9 (9.4 %)
Total	36 (37.5 %)

As a treatment for muscle invasive bladder cancer, radical cystectomy remains a highly morbid operation with complication rates of 40-60% and mortality rates as high as 9% in the first 90 days after surgery.^[19, 20] Albinini et al.^[21] have analyzed postoperative complications after laparoscopic radical cystectomy (LRC) and evaluated its risk factors in a large prospective cohort built by the ESUT across European centers involved in minimally invasive urology in the last decade. A total of 548 patients were available for final analysis, of which 258(47%) experienced early complications during the first 90 days after LRC. Infectious, gastrointestinal, and genitourinary were, respectively, the most frequent systems involved. Postoperative ileus occurred in 51/548 (9.3%) patients. A total of 65/548 (12%) patients underwent surgical re-operation, and 10/548 (2%) patients died in the early postoperative period. Increased BMI ($P=0.024$), blood loss ($P=0.021$), and neoadjuvant treatment ($P=0.016$) were significantly associated with a greater overall risk of experiencing complications on multivariate logistic regression. Long-term complications were documented in 64/548 (12%), and involved mainly stenosis of the uretero-ileal anastomosis or incisional hernias.

According to Gandaglia et al.,^[22] among 1094 patients undergoing radical cystectomy, rates of overall complications, transfusions, prolonged length of hospitalization, readmission, and perioperative mortality were 31.1%, 34.4%, 25.9%, 20.2%, and 2.7%, respectively. Body mass index represented an independent predictor of overall complications on multivariate analysis ($P=0.04$). Baseline comorbidity status was associated with increased odds of postoperative complications, prolonged operative time, transfusion, prolonged hospitalization, and perioperative mortality. In particular, patients with cardiovascular comorbidities were 2.4 times more likely to die within 30 days following cystectomy compared to their healthier counterparts ($P=0.04$). Men had lower odds of prolonged operative time and blood transfusions ($P\leq 0.03$). Finally, the receipt of a continent urinary diversion was the only predictor of readmission ($P=0.02$).

Radical cystectomy patients (n=2303) captured from NSQIP hospitals from January 1, 2006 to December 31, 2012 were analyzed by Lavallée et al.^[23] 1115 (48%) patients were over 70 years old and 1819 (79%) were male. Median hospital stay was 8 days (IQR 7-13 days). 1273 (55.3%) patients experienced at least 1 post-operative complication of which 191 (15.6%) occurred after hospital discharge. The most common complication was blood transfusion (n=875; 38.0%), followed by infectious complications with 218 (9.5%)

urinary tract infections, 193(8.4%) surgical site infections, and 223(9.7%) sepsis events. 73(3.2%) patients had fascial dehiscence, 82(4.0%) developed a deep vein thrombosis, and 67(2.9%) died. Factors independently associated with the occurrence of any post-operative complication included: age, female gender, ASA class, pre-operative sepsis, COPD, low serum albumin concentration, pre-operative radiotherapy, pre-operative transfusion >4 units, and operative time >6 hours ($P<0.05$). Complications, transfusions, readmission, and perioperative mortality remain relatively common events in patients undergoing radical cystectomy for bladder cancer.

Conclusion

Radical cystectomy with the Bricker ureterointestinal anastomosis allows us to obtain satisfactory functional results in the early and long-term periods after surgery, but the number of postoperative complications is still high. In our opinion, this is due to the imperfection of the analyzed ureterointestinal anastomosis, which is formed “end-to-side,” that promotes the development of ureterointestinal reflux. A reduced valve function of the Bricker ureterointestinal anastomosis can cause severe complications, such as kidney stones, recurrent pyelonephritis, and renal insufficiency. In this regard, the development of a new method for the urethra anastomosis with the tubular intestinal segment has important value.

Competing interests

The authors declare that they have no competing interests.

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Preperitoneal Blockade in the Treatment of Patients with Perforated Gastroduodenal Ulcers and Peritonitis

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Abstract

The objective of this study was to improve the results of surgical treatment for patients with perforated gastroduodenal ulcers and peritonitis (PGDU-P) by applying the preperitoneal blockade.

Materials and Methods: The study included 102 patients with perforated gastroduodenal ulcers (PGDU) complicated by peritonitis. Patients between 18 and 30 years were predominant. Pain was measured using the Visual Analog Scale (VAS) for Pain. The measurements of intra-abdominal pressure (IAP) by indirect infravesical tensometry were performed daily from the first day after the operation. Surgical interventions (laparotomy, laparoscopic suturing of PGDU, sanitation and drainage of the abdominal cavity) was performed under endotracheal anesthesia in all patients.

Patients were divided into two groups depending on the method of postoperative analgesia. Patients of Group 1 (n=62) were subjected only to systemic opioid analgesia (an intramuscular injection of 1% solution of Promedol 1ml 4 times a day). Patients of Group 2 were subjected to systemic opioid analgesia and catheterization of the preperitoneal space for infusion of 0.5% solution of Novocaine in the postoperative period.

Results: Postoperative analgesia using preperitoneal blockade after laparotomy and suturing of perforated gastroduodenal ulcers reduced the pain intensity by 2 times in comparison with conventional analgesia. The preperitoneal blockade after laparotomy in PGDU-P patients promotes the effective reduction of intra-abdominal hypertension (IAH) for 2 days. The comparative evaluation of the incidence of the early postoperative complications showed that using preperitoneal blockade contributed to significantly reducing the complications in Group 2. Postoperative mortality was 1.6% in Group 1 and 0 in Group 2. The average length of stay was reduced by approximately 3 days in Group 2 compared to traditional anesthesia. (**Int J Biomed. 2016;6(2):114-118.**)

Key Words: laparotomy • perforated gastroduodenal ulcers • peritonitis • preperitoneal blockade

Introduction

In the Russian Federation, the number of patients with complicated peptic ulcer disease (PUD) shows no tendency to decrease. The incidence of perforated gastroduodenal ulcers (PGDU) ranges from 4% to 30%, and the mortality rate is between 5% and 18%.^[1-5] Annually, the number of patients who need surgical intervention for PUD complicated by perforation is about 7.5 to 13 per 100,000 adult population.^[1,2,6] Mortality in PUD patients in Russia is 30,000 or more people per year; the temporary disability after surgery is between 30 and 45 days.^[1,2]

Despite the widespread adoption of minimally invasive technologies in the surgery of perforated peptic ulcer disease with peritonitis, laparotomy remains the most common prompt access.^[1,2,6,7] Laparotomy and surgical procedures in the abdomen are accompanied by traumatization of the abdominal muscles and peritoneum (the richly innervated tissues), which leads to a marked pain syndrome in the postoperative period. Pain triggers physiological responses that negatively affect the functioning of the organs and systems, with development of several pathophysiological repercussions, such as prolonged paralytic ileus.^[6-12]

Traditional analgesia with the most commonly used opioid analgesics is often accompanied by side effects and worsens the postoperative period.^[1,2,6,10,12] Currently, some authors consider catheterizing the surgical wound by infusing local anesthetics in the preperitoneal space as the most effective pain relief after laparotomy.^[6,8-13] The foregoing

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indicates the need for further studies of the postoperative analgesia for patients with PGDU and peritonitis (PGDU-P) after laparotomy.

The main objective of our study was to improve the results of surgical treatment for patients with PGDU-P by applying the preperitoneal blockade.

Materials and Methods

The retrospective study was performed in the period from 2001 to 2015. The number of patients for primary selection was 190; the number of patients included in the subsequent analysis was 102.

One hundred and ninety patients with PGDU-P, aged from 18 to 74 years, underwent laparotomy, laparoscopic suturing of PGDU, and sanitation and drainage of the abdominal cavity in the surgical departments at the Ulyanovsk Regional Clinical Center of Specialized Types of Medical Aid in the period from 2001 to 2015.

Inclusion criteria were age 18 years and older, male and female, perforated pyloroduodenal peptic ulcer, laparotomy, PUD history up to 3 years, the reactive and toxic stage of peritonitis. Exclusion criteria were video-laparoscopy, perforated pyloroduodenal combined with concomitant ulcerogenic complications, toxic and terminal stage of peritonitis, cancer, myocardial infarction, and acute cerebrovascular accident.

This study included 102 patients (100/98% men and 2/2% women) with PGDU-P (Table 1). Patients between 18 and 30 years were predominant. All patients were admitted to hospital with duration of perforation between 12 and 16 hours before admission. Standard examination included general clinical, laboratory and special instrumental investigations (X-ray, endoscopy, ultrasound, video-endoscope, histological research methods). Pain was measured using the Visual Analog Scale (VAS) for Pain. The laboratory examination included the complete blood count, blood chemistry, urine diastase. Leukocyte intoxication index (LII) was calculated according to V. K. Ostrovsky (1983).

Table 1.

Demographic characteristics of patients enrolled in this study (n=102)

Age (y)	Gender		Number of patients
	Male	Female	
18 - 30	38 (37.3%)	2 (2%)	40(39.3 %)
31 - 40	29 (28.4%)	-	29(28.4%)
41 - 50	18 (17.6%)	-	18(17.6%)
51 - 60	12 (11.8%)	-	12(11.8%)
> 60	3 (2.9%)	-	3(2.9%)
Total	100 (98%)	2 (2%)	102(100 %)

The measurements of intra-abdominal pressure (IAP) by indirect infravesical tensometry were performed daily from the first day after the operation. Measurements were performed in cm H₂O and converted to mmHg (1 mmHg = 1.36 cmH₂O).

Intra-abdominal hypertension (IAH) was identified at IAP greater than 12 mmHg. According to M. Sugrue and K. M. Hillman (1998),^[14] IAH was identified at IAP greater than 12 mmHg.

Surgical interventions (laparotomy, laparoscopic suturing of PGDU, sanitation and drainage of the abdominal cavity) was performed under endotracheal anesthesia in all patients.

Patients were divided into two groups depending on the method of postoperative analgesia. Patients of Group 1 (n=62) were subjected only to systemic opioid analgesia (an intramuscular injection of 1% solution of Promedol 1ml 4 times a day). Patients of Group 2 were subjected to systemic opioid analgesia and catheterization of the preperitoneal space for infusion of 0.5% solution of Novocaine in the postoperative period.

The method was performed as follows: Before suturing of laparotomic wound, we formed tunnels in the preperitoneal space along the full length of the laparotomic wound left and right at a distance of 1.5-2.0 cm from its edges. In the left and right tunnels, plastic catheters with a few holes were inserted. The cannula (the external opening) of the catheter was fixed on the anterior abdominal wall. The catheters were fixed to the peritoneum using absorbable suture material. In the postoperative period, a 0.5% solution of Novocaine was injected through catheters for pain relief every 3 hours for 3 days (RF patent №2400259; a priority from 02.17.2009).^[13]

During the postoperative period, adequate fluid resuscitation was performed. Correction of water-salt balance was carried out under the control of the content of potassium, calcium, and sodium in the blood plasma. For parenteral nutrition, protein hydrolysates and glucose-insulin-potassium mixture were administered.

Nasogastric tube was left in place for at least 24 h after surgery. Prophylaxis and treatment of intestinal paresis was performed by administration of neostigmine methylsulfate (1ml of 0.05% solution subcutaneously 2 times a day) and hypertonic solution of sodium chloride (60-80 ml intravenously 1-2 times a day). In order to prevent septic complications, we administered intravenously third-generation cephalosporins.

The study was conducted in accordance with ethical principles of the Declaration of Helsinki. It was approved by the by Ethics Committee at the Ulyanovsk Regional Clinical Center of Specialized Types of Medical Aid. Written informed consent was obtained from all participants.

Statistical analysis was performed using the statistical software «Statistica». (v6.0, StatSoft, USA). Group comparisons with respect to categorical variables are performed using chi-square tests with the Yates' correction or, alternatively, Fisher's exact test when expected cell counts were less than 5. A probability value of $P < 0.05$ was considered statistically significant.

Results

In assessing the effectiveness of preperitoneal blockade, a high degree of pain relief was found in the patients of Group 2 (3.3±0.4 points) (Tab. 2). Postoperative analgesia

using preperitoneal blockade after laparotomy and suturing of perforated gastroduodenal ulcers reduced the pain intensity by 2 times in comparison with conventional analgesia.

Table 2.

Total pain scores by Visual Analog Scale for Pain

Variable	Group 1(n=62)	Group 2 (n=40)
VAS, score	6.8±0.5	3.3±0.4*

**P*-value <0.05 between Groups

IAH was detected in all patients in both groups starting from the third postoperative day. According to IAH severity, patients were distributed as follows: In Group 1, Grades I, II and III of IAH were determined in 18(29%), 36(58.1%), and 8(12.9%) of patients, respectively. In Group 2, IAH Grades I and II were detected in 28(70%) and 12(30%) of patients; we did not observed IAH Grade III in this Group (Tab. 3).

Table 3.

Distribution of patients by degree of intra-abdominal hypertension

Grade	Group 1(n=62) (n/%)	Group 2 (n=40) (n/%)	<i>P</i> -value
I	18/29	28/70	<0.001
II	36/58.1	12/30	<0.01
III	8/12.9	-	<0.05
IV	-	-	

In patients with IAH Grades II and III (Group 1), the level of IAP decreased from 19.9±0.3 mmHg (the 3rd day) to 15.3±0.2 mmHg (the 6th day) and from 22.3±0.4 mmHg (the 3rd day) to 17.4±0.4 mmHg (the 7th day), respectively (*P*<0.05). In Group 2, we observed a significant decrease in the IAP level in patients with IAH Grades I and II from 14.8±0.2 mmHg (the 3rd day) to 12.1±0.3 mmHg (the 5th day) and from 19.4±0.3 mmHg (the 3rd day) to 15.1±0.2 mmHg (the 5th day), respectively (*P*<0.05). The preperitoneal blockade after laparotomy in PGDU-P patients reduced the IAP level by 2.7 mmHg at IAH Grade I and by 4.3 mmHg at Grade II for 2 days.

In Group 1, the first bowel movement (the first stool) we observed was at day 6.5±0.3, in Group 2 – at day 4.2±0.2. On the 2nd day of intervention, LII was 10.4±0.3 CU in Group 1 (Table 4) and 8.1±0.2 CU in Group 2 (*P*<0.05); at the 6th day, LII was also significantly lower in Group 2 than in Group 1; by the 10th day, LII was within normal range in all patients.

Table 4.

Dynamics of LII in the postoperative period

Group	LII (CU)		
	The 2 nd day	The 6 th day	The 10 th day
Group 1 (n=62)	10.4±0.3	8.2±0.3*	2.3±0.2*
Group 2 (n=40)	8.1±0.2^	6.0±0.2*^	2.2±0.2*

**P* – value <0.05 versus the initial data

^ *P*-value <0.05 between groups

Thus, the superior efficiency of preperitoneal blockade was confirmed by significant differences between two Groups in the severity of intra-abdominal hypertension and time of data normalization.

The number of the early postoperative complications in Groups was as follows: gastrostasis was detected in 34(54.8%) patients in Group 1 and 16(40%) patients in Group 2; dynamic ileus in 25(40.3%) of patients in Group 1 and 12(30%) patients in Group 2; mechanical ileus (early adhesive disease of the abdominal cavity) in 1(1.6%) patient in Group 1 (relaparotomy was performed), this complication we did not observed in Group 2; pneumonia - in 10(16.1%) patients in Group 1 and 2(5%) patients in Group 2; seroma and suppuration of postoperative wound - in 14(22.6%) patients in Group 1 and 3(7.5%) patients in Group 2; thromboembolism and acute cardiovascular failure were identified only in one patient (1.6%) in Group 1 (Tab. 5).

Table 5.

Early postoperative complications in PGDU-P patients

Early postoperative complications	Group 1 (n/%)	Group 2 (n/%)	<i>P</i> -value
Gastroptosis	34/54.8	16/40	> 0.05
Dynamic ileus	25/40.3	12/30	> 0.05
Mechanical ileus (early adhesive disease of the abdominal cavity)	1/1.6	-	
Pneumonia	10/16.1	2/5	> 0.05
Thromboembolism and acute cardiovascular failure	1/1.6	-	
Infected seroma or suppuration of postoperative wound	14/22.6	3/7.5	< 0.05

The comparative evaluation of the incidence of the early postoperative complications showed that using preperitoneal blockade contributed to significantly reducing the complications in Group 2. Postoperative mortality was 1.6% in Group 1. Thromboembolism and acute cardiovascular failure was the cause of postoperative mortality in 1(1.6%) patients in Group 1. In Group 2, postoperative mortality was absent.

The duration of hospital treatment was 14.5±0.3 days in Group 1 and 11.2±0.2 days in Group 2 (*P*<0.05); the average length of stay was reduced by approximately 3 days compared to traditional anesthesia.

Discussion

Traditional laparotomy in patients with perforated gastroduodenal ulcers and peritonitis contributes to the long-term pain syndrome in the postoperative period, which disrupts the function of many organs and systems.^[1,2,6,10,11] Pain that occurs after surgery has visceral and somatic components.^[1,2,6,10,13] Somatic pain after laparotomy is determined by the direct traumatization of tissue during surgical access. It is known that chronic stimulation of spinal afferents from visceral organs may elicit pain, hyperalgesia and allodynia in the

referred zones of the deep somatic tissues (skin, subcutaneous tissue, muscles and fascia).^[15] Reduced visceral pain signaling within the spinal cord has been shown to reciprocally diminish cutaneous sensitization.^[16]

Noiceptive pain is caused by irritation of nociceptors in the parietal peritoneum.^[1,2,6,10,13] T. Brennan et al. showed^[17] that the blockade of parietal afferents may reduce spinal dorsal horn neuron sensitization thereby providing postoperative analgesia that outlasts the duration of wound infusion. Furthermore, animal studies have shown that parietal pain may sensitize neurons in the spinal cord to visceral colonic pain.^[18-19] This sensitization most likely reflects convergence of afferent information from the gut and somatic system within the spinal cord (heterosynaptic facilitation).^[20] Thus, the peritoneum and the deep muscular layer play a crucial role in the pain induced by abdominal incisions. This assumption is further supported by the failure of epidural analgesia when metameric level is not high enough to block peritoneal nociceptive influx, even after lower abdominal surgery.^[21]

Therefore, it cannot be excluded that blockade of parietal pain influx may even contribute to a reduction of the visceral component of pain.^[22] The preperitoneal infusion of ropivacaine has recently been shown to prevent mechanical and visceral sensitivity following laparotomy in an animal model. High-dose ropivacaine administered via a preperitoneal infusion or systemic boluses had the same effect on mechanical and visceral sensitivity after laparotomy.^[23] According to Beaussier M et al.,^[22] preperitoneal continuous infiltration of 0.2% ropivacaine at 10 ml/h during 48 h was an effective method to relieve pain after open colorectal surgery. It reduced morphine consumption and accelerated the postoperative recovery.

Time to ileus resolution after abdominal surgery is one of the most important factors contributing to the duration of hospital stay. A number of pathogenic mechanisms have been proposed for postoperative Ileus.^[24-25] Earlier resolution of postoperative ileus has been reported in studies of continuous local anaesthetic wound infusion.^[22,26,27]

Our results show that the introduction of 0.5% solution of Novocaine in the preperitoneal space after laparotomy in PGDU-P patients promotes blocking the parietal and tissue pain receptors, which ensures a high degree of pain relief. We believe that the significant decrease in the number of such early postoperative complications as a dynamic ileus and wound inflammations is associated with adequate anesthesia during preperitoneal blockade. In agreement with other reports on continuous local anesthetic wound perfusion, no local complications were observed.^[22,28]

Conclusion

Postoperative analgesia using preperitoneal blockade after laparotomy and suturing of perforated gastroduodenal ulcers reduced the pain intensity by 2 times in comparison with conventional analgesia. The preperitoneal blockade after laparotomy in PGDU-P patients promotes the effective reduction of IAH for 2 days.

Competing interests

The authors declare that they have no competing interests.

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Combined Antirelapse Therapy in Patients with Schizoaffective Disorder: A Prospective Cohort Study

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Abstract

Background: In most studies, patients with schizoaffective disorder (SAD) are often combined into one group along with schizophrenia patients or less commonly with those suffering from affective disorders, which makes it difficult to obtain data about the peculiarities of SAD treatment. Articles dedicated to SAD treatment in the interictal period are rare.

Methods and Results: The prospective cohort study was conducted from 2011 to 2015. The study involved 86 patients diagnosed with SAD according to ICD-10. Patients received neuroleptics (NLs) as antirelapse therapy for 2 years (NL therapy); then mood stabilizers (MSs) were added to the antirelapse treatment (NL+MS therapy). The results of this combined therapy with MSs were evaluated after 2 years of treatment. Our results suggest that the use of combination therapy that includes antipsychotics and MSs leads to maintenance of a higher quality remission. Remission becomes more prolonged and affective swings less pronounced, resulting in improved quality of life in SAD patients. Improving the quality of remission can be attributed to the following characteristics of the combined therapy: a) the use of lower doses of neuroleptics; b) a reduction in the frequency and severity of mood swings; and c) an increase in patient compliance.

Conclusion: The use of combined pharmacotherapy including antipsychotics and MSs produces a longer, high-quality remission. The inclusion of MSs in the scheme of treatment increases the patient adherence to a medication regimen. The use of MSs in combination therapy reduces affective fluctuations, thereby increasing the probability of maintaining remission with complete symptom relief. (*Int J Biomed.* 2016;6(2):119-123.)

Key Words: schizoaffective disorder • antirelapse therapy • mood stabilizers • high-quality remission

Introduction

According to various studies, the prevalence of schizoaffective disorder (SAD) ranges from about 0.2% to 1.1% of the population worldwide.^[1] This diversity in estimates of the prevalence is due to variations in the diagnostic criteria used by the authors; however, most agree on the criteria of ICD-10 and DSM-5.^[2,3] Until now, researchers have not decided on the independence of this disorder, and SAD is often included in the spectrum of schizophrenic disorders;

rarely, it is referred to as bipolar disorder.^[3-7] According to some studies, an overlap between schizophrenia, SAD and bipolar affective disorder type I was observed at the evaluation of genetic and biological parameters.^[1,8,9] However, there are a number of modern clinical, molecular-genetic, biochemical and histological studies confirming the validity of segregation of such a nosological unit as schizoaffective disorder. ^[1,3,10-13] Researchers distinguish several SAD features, such as greater frequency of hospitalizations of SAD patients in comparison with patients suffering from schizophrenia and, at the same time, a high potential for recovery and social adaptation of patients with SAD.^[13,14]

Currently, the main objective of mental health care is not only the elimination of mental illness symptoms, but also the restoration of the original level of social functioning and

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quality of life, if possible. In this regard, particular attention is paid to the maintenance of high-quality remission.

Remission quality is defined by its duration, the presence or absence of residual symptoms, and the level of social adaptation. Preventive treatment can improve the quality of SAD remission.^[13] There is an ongoing dispute about necessity and duration of maintenance therapy in SAD. The most commonly administered treatment includes antidepressants and antipsychotics.^[1,14,15] Possibilities of preventive treatment expanded considerably after the introduction of mood stabilizers (MSs).^[1,3,19] The preference is currently given to atypical antipsychotic medications which have a mood stabilizing effect in addition to an antipsychotic one.^[16,17,20] The most frequently prescribed are second-generation antipsychotics, but the high cost and side effects (weight gain and sexual dysfunction) lead to patients with SAD abandoning treatment.^[16-18] The combination of antipsychotics and MSs may be effective and more easily tolerated by patients, reducing the overall neuroleptic load as a result. Articles dedicated to SAD treatment in the interictal period are rare.^[9,20]

In most studies, SAD patients are often combined into one group along with schizophrenia patients or less commonly with those suffering from affective disorders,^[18-20] which makes it difficult to obtain data about the peculiarities of SAD treatment. Therefore, it became necessary to investigate the influence of different types of therapy on the quality of remission in schizoaffective disorder.

Materials and Methods

The prospective cohort study was conducted from 2011 to 2015. Patients were observed in S.S. Korsakov Clinic of Psychiatry of I.M. Sechenov First Moscow State Medical University (MSMU) and in the Moscow outpatient psychiatric clinic No7.

Patient selection was carried out after the approval by the ethics committee of I.M. Sechenov First MSMU. After complete description of the study, written informed consent was obtained from all patients.

The study involved 86 patients (50/58.13% men and 36/41.87% women) diagnosed with SAD according to ICD-10. The duration of the disease ranged from 4 to 32 years. The average age of patients was 31.17±6.2 years at the start of the survey and 25.53±7.93 years at diagnosis of the disease.

Exclusion criteria were presence of significant physical disorders, exogenous organic disorders and substance dependence.

The first survey was carried out during one week after patients were discharged from a psychiatric hospital. To study the characteristics of SAD remission, clinical-psychopathological and clinical follow-up survey with a structured interview were conducted. The hospital discharge reports were also examined. Later, patients visited the clinic every month, and if they did not come, a nurse communicated with them in order to find out the reason for the absence. In case of an exacerbation, patients were re-admitted to the hospital and were observed again after discharge.

In the study, patients received neuroleptics (NLs) as

antirelapse therapy for 2 years (NL therapy); then MSs were added to the antirelapse treatment (NL+MS therapy). The results of this combined therapy with MSs were evaluated after 2 years of treatment. Patients with NL+MS therapy were also divided into 3 subgroups according to the MS incorporated in the therapy (LC - lithium carbonate, CBM - carbamazepine, VA - valproic acid).

Patients were surveyed by clinical and psychopathological methods and a structured interview; we also conducted interviews with patients' relatives and studied patients' medical records.

By the beginning of this study, the remission in patients was either with complete reduction of psychopathology or we detected anxiety, depressed mood, and residual delusions.

Patients were treated with typical neuroleptics from butyrophenone (haloperidol), piperazine phenothiazines (trifluoperazin) groups, atypical antipsychotics group of benzodiazepines (clozapine, olanzapine), benzisoxazole derivatives (risperidone).

Tricyclic (amitriptyline, clomipramine) and heterocyclic (mirtazapine) antidepressants, selective serotonin reuptake inhibitors (paroxetine, fluvoxamine), and antiparkinsonian drugs (trihexphenidyl) were prescribed if necessary.

More details on drugs used are given in Tables 1 and 2.

Statistical analysis was performed using the SPSS for Windows. Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean (M) and standard error of the mean (SEM) for continuous variables. Student's unpaired and paired t-tests were used to compare two groups for data with normal distribution. Comparisons between three groups were performed with the one-way ANOVA with Tukey's post-hoc test. Group comparisons with respect to categorical variables are performed using chi-square test. A probability value of $P < 0.05$ was considered statistically significant.

Table 1.

Doses (mg) of antipsychotics used for SAD patient treatment

Medication	NL therapy (n=86)		NL+MS therapy (n=86)	
	M±SEM	Mode	M±SEM	Mode
Haloperidol	9.68±1.22	15	5.14±2.32	4.5
Trifluoperazin	23.01±3.35	25	27.43±9.47	25
Clozapine	197.46±33.53	200	108.79±9.97	100
Olanzapine	18.86±1.98	20	5.98±2.76	5
Risperidone	4.13±0.22	4	3.33±0.57	2

Table 2.

Mood stabilizers (mg) used for antirelapse therapy for SAD patients (Group NL+MS)

Medication	Mean	Mode	Minimum value	Maximum value	Standard Deviation	Number of patients
LC	743.75	900	500.000	900.000	151.20	40/46.5
CBM	376.92	300	100.000	1,200.00	341.94	17/19.8
VA	622.72	600	100.000	1,200.00	385.98	29/33.7

Results

Treatment with only NLs was associated with a shorter remission (less than 1 year) compared to treatment with NLs plus MSs. Adding MSs to the therapy significantly increased the mean duration of remission (Table 3).

In order to study alterations in the ratio of hospitalization length to the duration of remission under the influence of various types of antirelapse therapy, we used the efficiency ratio (ER), the integral indicator reflecting the overall antirelapse effect of different medical regimens. The lower the score, the longer the remission and the shorter the subsequent hospitalization (ie, the medical regimen has a more pronounced preventive effect.) In NL therapy, ER was 0.34. In NL+MS therapy, ER was significantly lower compared to all other types of NL therapy. In patients receiving a medical regimen that comprised lithium carbonate, the efficiency ratio was 0.21. ER in patients who received carbamazepine and valproic acid was 0.26 and 0.17, respectively. Consequently, valproic acid has the best preventive effect; however, such results may be related to features of the patient sample. At the same time, according to recent data, valproate has a preventive effect not just against maniacal, but also against depressive episodes, which may explain their advantage over the other drugs.

In the study of the impact of MS antirelapse therapy on the risk of exacerbations in 6, 12 and 24 months of treatment, the following results were obtained: In the first 6 months of preventive treatment, the use of MSs reduced the risk of exacerbations by 1.7 times; in patients taking MS treatment for 12 months and others for 2 years, this risk was 1.6 and 1.7 times less than that of patients treated with only NLs.

Thus, during the first 2 years of MS preventive treatment, the risk of disease exacerbation remained constant and was lower than in patients not receiving such therapy. During the first 3 years following the SAD attack, the risk of exacerbation in patients treated with NLs+MSs was 1.6 times less than that of patients treated with only NLs (Table 3).

During NL+MS therapy, the proportion of patients without residual symptoms increased twofold, mainly due to the reduction in the number of patients with affective symptoms (Table 4).

It was also found that MSs have a pronounced antisuicidal effect: absolute risk to commit suicidal acts in patients taking MSs was 0.042; in those who did not receive these drugs - 0.235. The odds ratio for patients receiving and not receiving mood stabilizers was 0.014 ($P=0.02$).

Furthermore, the application of MSs resulted in an increase in the SAD patient compliance. This was due to a decrease in the severity of mood swings and a reduction of irritability and neuroleptic total load in chlorpromazine equivalents. High neuroleptic load is known to cause side effects that often lead to abandonment of treatment, irregularity in reception of drugs, and a search for specialists in alternative medicine. It turned out that supplementation of MSs can reduce the neuroleptic load about 1.5 to 2 times (Table 5).

Patients treated with NL+MS were rarely treated with antiparkinsonians or tranquilizers (Table 6).

When analyzing the structure of exacerbations in examined patients after different types of preventive treatment, we found that the application of MSs in combination with other drugs clearly reduced the proportion of episodes with manic affect (Table 7).

Table 3.

The duration of remission and the average length of hospital stay for different types of therapy

	NL/LC+ (n=40)	<i>P</i>	NL/LC- (n=40)	NL/CBM+ (n=17)	<i>P</i>	NL/CBM- (n=17)	NL/VA+ (n=29)	<i>P</i>	NL/VA- (n=29)	ANOVA	
										NL/MS+	NL/MS-
Duration of remission (days)	338.9±22.1	0.0038	231.48±15.9	440.9±38.7	0.0049	233.6±42.9	522.2±101.1	0.0045	212.2±36	$F=2.5129$ $P=0.0872$	$F=0.1587$ $P=0.8535$
Length of hospital stay (days)	66.1±6.9	0.2190	73.2±9.3	69.0±10.7	0.5831	68.5±12.8	84.5±13.4	0.6513	72.78±19.9	$F=0.9929$ $P=0.3749$	$F=0.0231$ $P=0.9772$

Table 4.

Residual symptoms after remission on the background of various types of antirelapse therapy

Variable	NL (n=86)	<i>P</i>	NL+MS (n=86)	NL+LC (n=40)	NL+CBM (n=17)	NL+VA (n=29)	<i>P</i>
No psychopathological symptoms	18/(20.9%)	0.0000	68/(79.1%)	34/(85.0%)	13/(76.5%)	21/(72.4%)	0.4283
Subdepression	40/(46.5%)	> 0.05	46/(53.5%)	30/(75.0%)	5/(29.4%)	11/(37.9%)	0.0008
Some delusional thinking	39/(45.3%)	> 0.05	47/(54.6%)	32/(80.0%)	6/(35.3%)	9/(31.0%)	0.0000
Combination of affective disorders with delusions	41/(47.6%)	> 0.05	45/(52.3%)	30/(75.0%)	5/(29.4%)	10/(34.5%)	0.0004

Table 5.

Total neuroleptic load in chlorpromazine equivalent (CPZE) on the background of various types of antirelapse therapy

Variable	NL/LC+ (n=40)	P	NL/LC- (n=40)	NL/CBM+ (n=17)	P	NL/CBM- (n=17)	NL/VA+ (n=29)	P	NL/VA- (n=29)	ANOVA	
										NL/MS+	NL/MS-
CPZE, mg	170.00±35.9	0.001	336.7±29.1	218.12±56.8	0.004	348.56±46.9	226.22±63.7	0.004	316.8±56.2	F=0.4110 P=0.6643	F=0.1117 P=0.8891

Table 6.

Treatment with antiparkinsonians and tranquilizers on the background of different types of therapy

Group	Antiparkinsonian drugs			Tranquilizer drugs		
	No	P	Yes	No	P	Yes
NL therapy	35/(40.7%)	0.01	51/(59.3%)	66/(76.7%)	0.000	20/(23.2%)
NL+MS therapy	61/(70.9%)	0.000	25/(29.1%)	79/(91.9%)	0.000	7/(8.1%)
P	0.000		0.000	0.006		0.006

Table 7.

The structure of exacerbations in examined patients after different types of preventive treatment

Episode type	NL n=86	P	NL+MS n=86	NL+LC n=40	NL+CBM n=17	NL+VA n=29	P
Depressive	18/(20.9%)	0.0000	66/(76.7%)	34/(85.0%)	6/(35.3%)	26/(89.6%)	0.0000
Manic	68/(79.1%)	0.0000	20/(23.2%)	6/(15.0%)	11/(64.7%)	3/(10.3%)	0.0000

According to our data, patients receiving MSs in their therapy scheme were 5 times more likely to adhere to their medical regimen (Table 8). Thus, we can conclude that the inclusion of MSs in the scheme of treatment increases the patient adherence to a medication regimen.

Table 8.

Adherence to medical regimen in different types of antirelapse treatment

Variable	NL (n=86)	P	NL+MS (n=86)
Refusal of medication or irregular use of medication	64/(74.4%)	0.0000	30/(34.9%)
Regular use of medication	22/(25.6%)	0.0000	56/(65.1%)

Discussion

Our results suggest that the use of combination therapy that includes antipsychotics and MSs leads to maintenance of a higher quality remission. Remission becomes more prolonged and affective swings less pronounced, resulting in improved quality of life in SAD patients and achieving the best results in the restoration of the previous level of social functioning. Improving the quality of remission can be attributed to the following characteristics of the combined therapy: a) the use

of lower doses of neuroleptics; b) a reduction in the frequency and severity of mood swings; and c) an increase in patient compliance.

The marked increase in adherence to recommendations in SAD patients using a combination therapy was determined by several factors: a) the thymostabilizing effect, which leads to a more adequate patient assessment of their own condition; b) reduction in total neuroleptic load, thereby a reduction in the number and severity of side effects, as well as an opportunity to reduce the frequency of taking the drugs to the morning and evening in order to avoid taking them during working hours (this may explain why some authors have noted a decrease in irritability of patients after MS appointment). MSs have shown high efficacy in the prevention of relapses in SAD patients, reducing the likelihood of an exacerbation by 1.7 times depending on the duration of therapy, according to our data. It is also important to note that the MS appointment has a strong antisuicidal effect, reducing this risk by 5.6 times. This is important because the probability of committing suicide during remission is highest and therefore the prevention activities in this period gain practical value.

Conclusion

In sum, we can conclude: 1) the use of combined pharmacotherapy including antipsychotics and MSs produces a longer, high-quality remission; 2) there are no statistically

significant differences in the impact of different groups of MSs on the average duration of remission; 3) the inclusion of MSs in the scheme of preventive treatment has no effect on the average length of subsequent hospitalization; 4) the use of MSs in combination therapy reduces affective fluctuations, thereby increasing the probability of maintaining remission with complete symptom relief; 5) MSs are effective in the prevention of suicidal behavior; 6) the use of MSs can reduce the necessity for tranquilizers and antiparkinsonians; 7) the inclusion of MSs in the scheme of treatment increases the patient adherence to a medication regimen.

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Effectiveness of Photodynamic Therapy in the Healing of Corneal Alkali Burn in Rats

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Abstract

In this study, we investigated the effect of photodynamic therapy (PDT) on the healing of corneal alkali burns in rats. The experiment was performed on 50 adult non-linear rats. Depending on the intervention, the animals were divided into 5 equal groups with 10 animals in each group: Group 1 included rats with intact eyes (the control group) and Groups 2 through 5 were experimental groups with experimental alkali burn (EAB). Group 2 consisted of rats subjected to instillation of 0.25% chloramphenicol solution; Group 3 consisted of rats subjected to photodynamic irradiation according to our scheme: 300 mJ (630 nm) for 3 minutes; Group 4 consisted of rats subjected to instillation of methylene blue (MB); Group 5 consisted of rats subjected to instillation of MB with subsequent photodynamic irradiation according to the described scheme.

During all periods of observation, the infiltration of the subcorneal zone was less pronounced in Group 5 than in the other groups and was represented mainly by round cells in the anterior chamber, iris, retina, and ciliary zone. The instillation of MB with subsequent photodynamic irradiation was the most effective in reducing the bacterial contamination

Thus, PDT with the photosensitizer methylene blue, in accordance with the designed exposure mode, provided the epithelialization and bacteriostatic effect during corneal repair after EAB. In conclusion, PDT improves a wound's healing process, which is expressed in the reduction of inflammatory infiltration and the promotion of corneal epithelialization. (*Int J Biomed.* 2016;6(2):124-127.).

Key Words: ocular surface • experimental alkali burn • photodynamic therapy • methylene blue

Introduction

Ocular chemical burns are the most urgent ophthalmic emergencies. Serious eye burns may destroy the entire corneal epithelium and extend into all eye structures, including conjunctiva, sclera, and vascular tract, which often results in a number of serious complications and adverse outcomes, despite active therapy.^[1]

The ocular surface is an integrated system^[2] with special features of regeneration after chemical burns; these features are not fully investigated and require experimental and histological studies.^[3-5] Despite the variety of therapeutic and surgical treatments, achieving stable epithelialization and preventing scar tissue developing at the site of an injury is often not possible, which leads to disruption of corneal transparency. In this connection, the search for new therapies

designed to stimulate cornea restoration and prevent the formation of scar tissue and glia, leading to blindness, is an urgent task of ophthalmology.^[6,7]

In recent years, several studies have demonstrated the effects of PDT in ophthalmology.^[3,8-13] PDT employs the different light-sensitizing drugs, termed a photosensitizer, and low intensity visible light which, in the presence of oxygen, combine to produce cytotoxic species. PDT has the advantage of dual selectivity, in that the photosensitizer can be targeted to its destination cell or tissue and, in addition, the illumination can be spatially directed to the lesion. PDT has previously been used to kill pathogenic microorganisms *in vitro*, but its use to treat infections in animal models or patients has not yet been much developed.^[14]

In Uzbekistan, a new device for ALT (Vostok) working in a range of 630 nm with a power of 5 watts has been developed and used in surgery, dentistry, and dermatology.^[15] Our early experimental studies revealed the optimal and safe dose (300 mJ [630 nm for 3 min]) for PDT in ophthalmology, which did not cause endogenous intoxication.^[4,5]

The objective of this study was to investigate the impact of the developed PDT doses on the processes of corneal epithelialization under an experimental alkali burn (EAB).

Materials and Methods

The experiment was performed on 50 adult non-linear rats weighing about 150 grams, contained in standard vivarium conditions. Eye examinations were conducted on all rats; rats were also subjected to bacterioscopic and histopathological examination.

A corneal alkali burn was generated in the right eye of each anesthetized rat. A piece of filter paper (5-mm diameter) soaked with 2.5% NaOH was applied to the center of the cornea for 5 seconds.^[7,16] As photosensitizer was used a 1% methylene blue (MB) aqueous solution (0.2 ml) applied just before irradiation. PDT was performed daily for 7 days using ALT equipment Vostok. Animal condition was monitored three times every day during 7 days post-injury.

Depending on the intervention, the animals were divided into 5 equal groups with 10 animals in each group: Group 1 included rats with intact eyes (the control group) and Groups 2 through 5 were experimental groups with EAB. Group 2 consisted of rats subjected to instillation of 0.25% chloramphenicol solution (2 drops 6 times per day); Group 3 consisted of rats subjected to photodynamic irradiation according to our scheme: 300 mJ (630 nm) for 3 minutes; Group 4 consisted of rats subjected to instillation of MB (2 drops 3 times per day); Group 5 consisted of rats subjected to instillation of MB (2 drops 3 times per day) with subsequent photodynamic irradiation according to the described scheme (300 mJ (630 nm) for 3 minutes). Rats of the control group underwent application of a 0.9% NaCl solution (2 drops 6 times per day) during 7 days.

The study was conducted in accordance with the principles of ARVO Statement for the use of animals in ophthalmic and visual research. Procedures for euthanasia (instant decapitation at the 3rd and 7th day of experiment) were performed according to MMRI Policy for the Humane Care and Use of Laboratory Animals in a manner consistent with the recommendations of the American Veterinary Medical Association (AVMA) Panel on Euthanasia.

Tissues of eye and orbit were fixed in 10% buffered formalin according to Lilly and embedded in paraffin. Sections 4 to 5 microns thick were stained with hematoxylin-eosin. For fluorescence microscopy, the dewaxed sections were stained with a 1% solution of acridine orange prepared on a base of phosphate isotonic buffer.^[17]

To study the bacterial flora, the test material was taken with a sterile cotton swab and transported to the laboratory within an hour. The technique of bacteriological examination has been described^[18] in the methodological recommendations. All isolated facultative-anaerobic microorganisms were identified up to the genus or species based on cultural, tinctorial, morphological, and biochemical properties. After corneal alkali burn was generated, the studied groups were not different in the number of eyes with bacterial infection (10 eyes in each group). Before treatment, the bacteriological examination revealed the

presence the following bacterial pathogens: *St. hemolyticus*, *St. epidermidis*, and *St. aureus*. *St. hemolyticus* was found in most cases (28%).

Light and fluorescence microscopy and photomicrography were performed with a BIOLAM I2 microscope with an MFI-5 photo-attachment and digital camera Canon 300D. Morphometry was performed using AxioVision 4.8.2 software.

Results were statistically processed using the software package «Biostatistics» for Windows (version 4.03) and Microsoft Office Excel 2007. Group comparisons with respect to categorical variables are performed using chi-square tests with the Yates' correction or, alternatively, Fisher's exact test when expected cell counts were less than 5. A probability value of $P < 0.05$ was considered statistically significant.

Results and Discussion

A day after EAB, all groups exhibited specific changes, which were manifested in a sharp edema of tissues around the wound. The burn zone was represented by detrital mass and infiltrated by neutrophilic leukocytes. Around the burn zone, we observed significant disturbances in the corneal structure: edema, infiltration, activation of keratocytes and neovasculogenesis. A moderate inflammatory response had developed in the sclera; the purulent-fibrinous exudate and polymorphocellular infiltration with a predominance of neutrophils were detected in the anterior chamber of the eye. Dramatically expanded vessels and polymorphocellular infiltration were identified in the ciliary body. On the surface of the retina, we observed a marked purulent-fibrinous exudate; the choroidal zone was also infiltrated by neutrophils. Moderate inflammation (swelling and infiltration) was observed in the conjunctival part of the eyelid. Moderate activation of secretory activity was identified in the lacrimal glands. Clinical manifestations in the form of redness, hypopyon, and edema of the ciliary body, iris and retina decreased in all groups under dynamic observation by the third day and especially by the seventh day, but the moderate leukocyte infiltration remained in Groups 2 and 4.

On the third day after EAB, in Groups 2 and 4, the cornea around the wound was infiltrated by neutrophilic leukocytes, and a bacterioscopic examination revealed the presence of a large number of coccal microflora (Table 1).

Table 1.

The results of bacteriological examination after intervention (n - the number of eyes/%)

Bacterial flora	Group 1	Group 2	Group 3	Group 4	Group 5	Total (n=50)	P-value
<i>St. hemolyticus</i>	2/14.3	4/28.6	2/14.3	5/35.8	1/7.1	14/28	0.6261
<i>St. epidermidis</i>	2/18.2	3/27.3	2/18.2	4/36.3	-	11/22	0.5874
<i>St. aureus</i>	1/14.3	3/42.8	1/14.3	2/28.6	-	7/14	0.7902
Mixed flora	3/16.7	5/27.8	3/16.7	5/27.8	2/11.1	18/36	0.8719
Number of eyes with bacterial infections							
n/%	8/47	10/25.6	8/20.5	10/25.6	3/7.7*	39/100	0.0065

*Fisher's exact test: $P\text{-value} = 0.003$ between Gr. 5 and Gr. 2 and 4

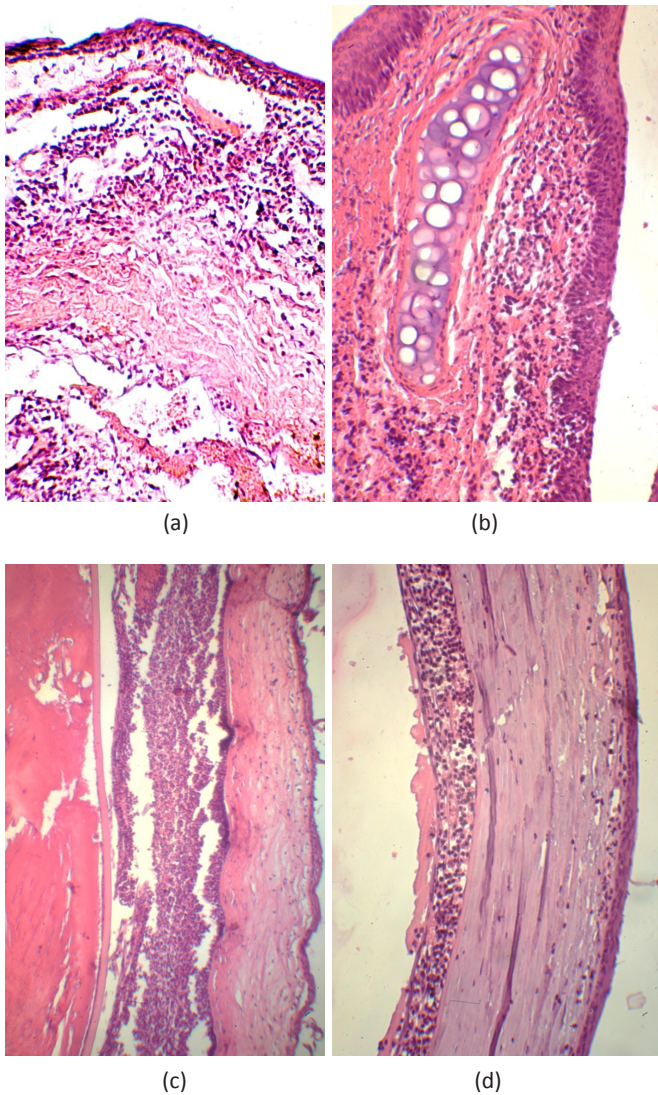


Fig. 1. Effect of PDT on the cornea and the eyelid after EAB in rats (H&E, 10x20)

- a) Severe edema and infiltration of the cornea in the affected zone (Group 2, the 3rd day)
- b) Moderate infiltration of the internal surface of the eyelid (Group 3, the 3rd day)
- c) Massive subcorneal infiltration and corneal edema (Group 4, the 7th day)
- d) Moderate subcorneal neutrophil infiltration (Group 5, the 7th day)

Polymorphocellular infiltration of the ocular structures, especially a massive accumulation of neutrophils, was observed in the area between the sclera and the vitreous body, as well as on the retina of most animals of these groups. In Group 5, starting from the third day of the experiment we observed a significant decrease in the number of detrital masses and a strong neutrophil infiltration in the affected zone. Around the burn zone on the cornea, as in the other groups, edema and disorders of the general architectonics were defined. However, activation of proliferative processes in the cornea and the degree of epithelialization of the wound surface were more intense in Group 5 (Fig.1).

By the seventh day after EAB, the phenomenon of neutrophil infiltration and bacterial contamination in all groups

was significantly lower, but the pronounced edema remained in Groups 2 and 4. According to bacterioscopic examination, a reduction in the degree of bacterial contamination was found in each group with varying degrees of effectiveness. The instillation of MB with subsequent photodynamic irradiation was the most effective in reducing the bacterial contamination (Table 1, Fig.2).

During all periods of observation, the infiltration of the subcorneal zone was less pronounced in Group 5 than in the other groups and was represented mainly by round cells in the anterior chamber, iris, retina, and ciliary zone (Fig.1 and 2).

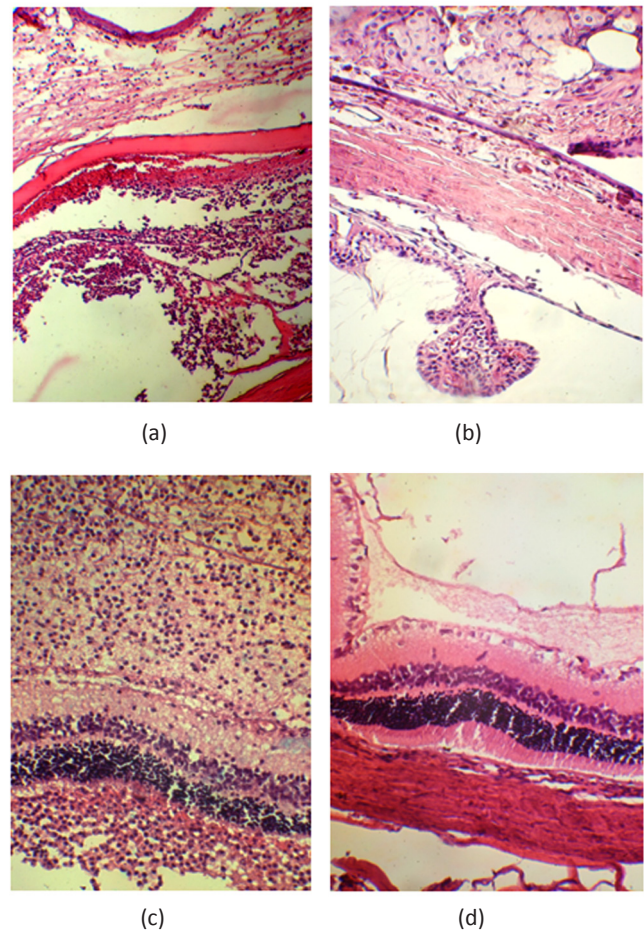


Fig. 2. Effect of PDT on the ciliary body and retina after EAB in rats (H&E, 10x20)

- a) Severe edema and leukocyte infiltration in the region of the ciliary body (Group 2, the 2nd day)
- b) Moderate hyperemia in the region of the ciliary body (Group 2, the 7th day)
- c) Total leukocyte infiltration of the retina (Group 4, the 7th day)
- d) Leukocyte infiltration is absent (Group 5, the 7th day)

It has been known since the first days of PDT, early in the last century, that certain microorganisms can be killed by the combination of dyes and light *in vitro*^[19] In the 1990s, it was observed that there was a fundamental difference in susceptibility to PDT between Gram-positive and Gram-negative bacteria. It was found that, in general, neutral or anionic photosensitizer molecules are efficiently bound to and

photodynamically inactivate Gram-positive bacteria, whereas they are bound, to a greater or lesser extent, only to the outer membrane of Gram-negative cells, but do not inactivate them after illumination. The high susceptibility of Gram-positive species is explained by their physiology.^[20]

In recent years interest in the antimicrobial effects of PDT has revived and it has been proposed as a therapy for a large variety of localized infections.^[20,21] Burns are particularly susceptible to infection due to the destruction of the cutaneous barrier and the fact that coagulated and denatured proteins present in the burn provide a nutritious environment for bacterial growth. Gram-positive bacteria and in particular *S. aureus* are early colonizers of burn wounds which makes the occurrence of multidrug resistant *S. aureus* a worrisome development.^[22,23] Superficial wound infections are potentially suitable for treatment by PDT because of the ready accessibility of these wounds for both topical delivery of the photosensitizer and light. Advantages of PDT include equal killing effectiveness regardless of antibiotic resistance, and a lack of induction of PDT resistance.

Conclusion

PDT with the photosensitizer methylene blue, in accordance with the designed exposure mode, provided the epithelialization and bacteriostatic effect during corneal repair after EAB. PDT improves a wound's healing process, which is expressed in the reduction of inflammatory infiltration and the promotion of corneal epithelialization.

Competing interests

The authors declare that they have no competing interests.

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Association of Chronic HBV Infection with Chronic Lymphoproliferative Disorders: A Review and Case Report

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Abstract

This article presents a clinical report on the associated course of chronic hepatitis B virus (HBV) infection with Castleman's disease (CD). We noticed the reactivation of previously latent chronic hepatitis B (CHB) with high replicative activity of HBV DNA during the treatment of lymphoproliferative disease. This clinical case dictates the need for pre-emptive therapy of HBV infection with nucleoside analogues in patients who are receiving chemotherapy. (**Int J Biomed.** 2016;6(2):128-132.)

Key Words: chronic hepatitis B • Castleman's disease • chemotherapy • rituximab • reactivation of viral infection

Introduction

The aim of our work was a clinical review of the case of HBV *reactivation* in a patient with Castleman's disease on the background of Rituximab therapy.

Infection caused by HBV is a serious public health challenge all over the world due to its high prevalence and high risk of chronicity with the development of liver cirrhosis and primary liver cancer. The number of HBV carriers in the world is estimated from 300 to 400 million people. The prevalence of HBV carriers ranges from 0.2% to 1% in Western Europe and the U.S. to 8% to 15% in the Far East, Middle East and Africa. In Russia, the prevalence of HBV infection is from 1.5% in the European areas to 5% in Yakutia and the Far East. The total number of people chronically infected with HBV in the Russian Federation is up to 5 million.^[1,2]

The Republic of Sakha (Yakutia) [the RS(Y)] is a disadvantaged region with respect to the incidence of CHB. According to the population register "Chronic viral hepatitis in the RS(Y)," on January 1, 2016, the number of registered

patients who were CHB and HBV carriers was 6,935 and 4,019, respectively, and the share of HBV infection in the overall structure of chronic hepatitis was 6.8%.^[3]

Patients with hematologic diseases are a group of individuals at high risk for HBV reactivation or development of acute HBV infection. This is primarily due to the development of secondary immunodeficiency on the background of the underlying disease, transfusion of the blood, and anti-tumor therapy.^[4] The big breakthrough in the treatment of lymphoproliferative diseases occurred after monoclonal antibodies were included in the therapy scheme. One of the first representatives of this group is rituximab. The effectiveness of rituximab was proven in international randomized trials in the treatment of non-Hodgkin's lymphoma.^[5]

Currently, rituximab is an integral part of the treatment of lymphoproliferative disorders. Rituximab is a chimeric anti-CD20 monoclonal antibody having the ability to specifically bind to the transmembrane antigen CD20 expressed on both normal and malignant B-lymphocytes. The drug causes a complement-dependent reaction, which results in the apoptosis of cells carrying the antigen CD20.^[6] Rituximab therapy leads to a reduction in the number of B-cells until zero level is reached.^[7]

The mechanism of reactivation of viral infection in the treatment of Castleman's disease has not been fully

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understood, but it has been suggested that rituximab plays the leading role. The treatment with rituximab leads to a sharp reduction in B cells in the blood. In study performed by Stasi et al.^[8] the effectiveness and side effects of rituximab treatment were investigated in a cohort of 25 individuals with chronic idiopathic thrombocytopenic purpura. Patients were scheduled to receive intravenous rituximab at the dose of 375 mg/m² once weekly for 4 weeks. Peripheral blood B cells, evaluated by flow cytometry as CD19⁺ cells, had a median baseline count of 189 × 10⁶/L (range, 56-418 × 10⁶/L). This count declined with treatment, to subnormal levels after the first dose for the majority of patients. Recovery of B cells started between 6 and 9 months, reaching normal values between 9 and 12 months. U. Specks et al.^[9] reported on the successful, compassionate use of the anti-CD20 chimeric monoclonal antibody rituximab in a patient with chronic, relapsing cytoplasmic antineutrophil cytoplasmic antibody (cANCA)-associated Wegener's granulomatosis. Complete remission was associated with the disappearance of B lymphocytes and cANCA.

M. Ghilmini et al.^[10] evaluated the effect of single-agent rituximab given at the standard or a prolonged schedule in patients with newly diagnosed, or refractory or relapsed mantle cell lymphoma. After induction treatment with the standard schedule (375 mg/m² weekly × 4), patients who were responding or who had stable disease at week 12 from the start of treatment were randomly assigned to no further treatment (arm A) or prolonged rituximab administration (375 mg/m²) every 8 weeks for four times (arm B). The trial enrolled 104 patients. After induction, clinical response was 27% with 2% complete responses. The lymphocytes subset analysis (performed excluding patients with baseline WBC > 10 × 10⁹/L who were suspected of having leukemic disease) showed a very early and important reduction of circulating B cells, while T-helper, T-suppressor, and natural killer cells remained approximately stable during the induction phase. Median B-cell levels returned to levels similar to baseline values after 9 months in arm A, while in arm B, the B-cell recovery had still not taken place after 12 months. The difference at 9 months was significant (median, 90.5 × 10⁶/L v 13.9 × 10⁶/L; *P* = 0.03).

Reactivation of HBV infection intensifies virus replication in patients with chronic infection or chronic carriers of HBV. The development of clinical and biochemical manifestation of hepatitis is possible in HBsAg carriers during immunosuppressive therapy, but most of the reactivation has been observed after discontinuation of treatment. A progressive increase in the concentration of serum HBV-DNA is the earliest and most accessible diagnostic indicator for HBV reactivation in clinical practice. At least a 10-fold increase, or exceeding the maximum level of 108 IU/mL, is a necessary diagnostic criterion. In the case of clinical-laboratory HBV reactivation, the probability of death is from 5% to 50% or more, but spontaneous recovery is possible. Especially poor prognosis occurs in hepatitis in patients with pre-existing liver cirrhosis, resulting in acute liver failure on the background of chronic liver failure.^[11]

In 2001, Dervite et al. reported, for the first time, a case of HBV reactivation in an HBsAg-negative patient who had

received rituximab combination chemotherapy.^[12]

T.Sera et al.^[13] and J.Law et al.^[14] have presented independently two patients with lymphoma in whom chemotherapy with rituximab resulted in fulminant hepatitis with a fatal outcome. Thus, J. Law et al.^[14] reported a 67-year-old man with B-cell lymphoma who developed hepatitis B reactivation following chemotherapy with cyclophosphamide, adriamycin, vincristine, prednisone and rituximab. Pre-chemotherapy, the patient was negative for HBsAg, positive for hepatitis B core antibody (anti-HBc) and weakly positive for hepatitis B surface antibody. Despite treatment with lamivudine, the patient died of fulminant hepatic failure. Authors concluded that patients who are negative for HBsAg but positive for anti-HBc are still at risk for reactivation of latent hepatitis B during and after chemotherapy and may be considered for prophylaxis.

In 2009, Yeo et al.^[15] reported that when systemic chemotherapy was used to treat 80 HBsAg-negative patients with malignant lymphoma, HBV reactivation was observed in 5 (6.25%) of them; all 5 of these patients were HBcAb- and/or HBsAb-positive, and rituximab and steroid combination chemotherapy had been performed in all 5 patients. Thus, it became evident that reactivation as a result of the combined use of chemotherapy with a high immunosuppressive effect, such as rituximab, or combination therapy with a steroid can occur even in HBsAg-negative patients with HBcAb and/or HBsAb positivity.^[16]

The number of reports regarding HBV reactivation following chemotherapy has been gradually increasing. Guidelines for the treatment of HBV reactivation following chemotherapy have been published by many groups: the American Association for the Study of Liver Disease (AASLD) Practice Guidelines in 2007;^[17] the National Institute of Health (NIH) Consensus Development Conference Management of Hepatitis B in 2008^[18,19] and the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines in 2009.^[20] All these guidelines are similar in principal. When chemotherapy is going to be performed, the prophylactic administration of an antiviral drug in HBsAg-positive patients is recommended, and the periodic monitoring of the HBV DNA level and deferred pre-emptive administration of an antiviral drug after the detection of conversion to HBV DNA positivity is recommended for HBsAg-negative patients with HBcAb and/or HBsAb positivity.

Currently, interferons are not used to prevent HBV-infection relapse. This is primarily due to their side effects, such as pancytopenia. Among the nucleoside analogues, the greatest experience has been gained in relation to lamivudine. However, one barrier to the success of long-term therapy is the emergence of drug-resistant mutants, which are frequently observed during treatment of CHB with lamivudine.^[20] Current guidelines, therefore, recommend that the most potent drugs with optimal resistance profiles (ie, entecavir [ETV] and tenofovir disoproxil fumarate [TDF]) should be used as first-line monotherapies in CHB.^[20-24] These two agents were approved by the US Food and Drug Administration (FDA) for the treatment of CHB on the basis of Phase III clinical study results in 2005 (ETV) and 2008 (TDF).

No clear evidence exists regarding the termination of the prophylactic administration of antiviral drugs. K. Ono et al. lead clinical example, when the premature cancellation of lamivudine resulted in a re-HBV infection reactivation.^[25] Once administration has been continued for 12 months after the completion of chemotherapy and a decrease in the ALT level to within the normal range and conversion to persistent HBV-DNA negativity have been achieved, the termination of the administration of the antiviral drug can be considered.^[16,26]

Castleman's disease, also known as angiofollicular lymph node hyperplasia, is characterized by non-clonal lymph node proliferation, and was first described by Benjamin Castleman in 1954.^[27] Pathologically, it is classified into three types: hyaline-vascular (HV), plasma-cell (PC) and mixed type.^[28] Castleman's disease is also categorized into two clinical types: unicentric and multicentric forms (UCD and MCD).^[29]

The pathogenesis of Castleman disease is not fully understood; however, the central roles of interleukin (IL) 6 in UCD and both IL-6 and human herpesvirus (HHV) 8 in MCD have been well described.^[30,31] Dysregulated and overproduced IL-6, particularly in patients with MCD, stimulates the production of acute phase reactants in the liver, resulting in constitutional symptoms, including fever, sweats, and fatigue, and laboratory abnormalities, such as anemia, elevated inflammatory markers, hypergammaglobulinemia, and hypoalbuminemia. IL-6 also stimulates B-cell proliferation and induces the expression of vascular endothelial growth factor and increased angiogenesis. IL-6 has emerged as a therapeutic target in Castleman disease based on its critical role in pathogenesis and driving of symptomatology.^[32,33]

When based on the clinical and pathological subtypes of Castleman's disease, clinical manifestation and management of the disease are distinct.^[34] Surgical resection remains the standard therapy for UCD, while systemic therapies are required for the management of MCD. Rituximab monotherapy is the mainstay of therapy; however, novel therapies targeting IL-6 (siltuximab [anti-IL-6 monoclonal antibody] and tocilizumab [anti-IL-6R humanized monoclonal antibody]) may represent a treatment option in the near future.^[33,35]

According to the Hematology Research Center of the RF Ministry of Health, 76 patients have been reported with Castleman's disease from 1996 to 2014.^[35] Accounting for CD patients in the RS(Y) was introduced in 2004. To date, five cases of CD have been registered in Yakutia, one of which (MCD) we present in this article.

Case presentation

A 55-year-old man considered himself ill since 2013, when on the background of overall health, headaches, sweating, fatigue, and weakness appeared, and then frequent exacerbations of chronic pyelonephritis were noted. In May 2014, he was hospitalized in the therapeutic department at YSCH of RS(Y) with suspected bronchopneumonia. Laboratory blood analysis was performed and the following results were obtained: ESR, 25 mm/hr; C-reactive protein (CRP), 196.14 mg/L; IgE, 1,439 IU/mL.

Examination revealed an increase in peripheral lymph nodes merging into conglomerates. Lymph nodes were dense and painless, some nodes were enlarged up to 2-3 cm in diameter. To clarify the diagnosis, the patient was transferred to the Oncology Center, where a biopsy of the right axillary lymph node was performed. Findings of histopathological and immunohistochemical examinations were compatible with the presence of PC type Castleman's disease (Fig. 1).

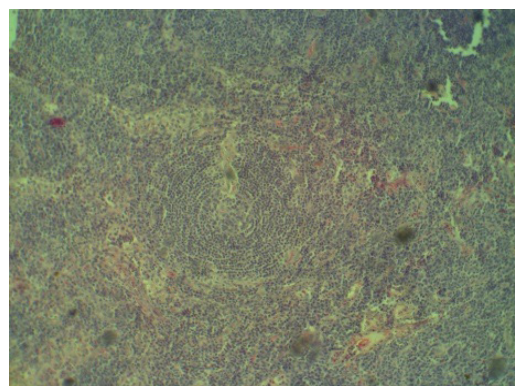


Fig. 1. Lymph node (x20). PC type Castleman's disease. IHC detection of mature CD138⁺ plasma cells.

To confirm the diagnosis and selection of therapy, the patient was hospitalized in the RCRC, named after NN Blokhin, where according to the histological study of the bone marrow with an immunohistochemical examination, he was diagnosed with HHV-8-negative multicentric Castleman's disease (PC type).

From August 2014 to March 2015, polychemotherapy (PCT) according to the R-VCD scheme (rituximab, bortezomib, cyclophosphamide, dexamethasone) was performed; the next course was applied on the 22nd day. During treatment, against the background of secondary immunodeficiency, the following complications were identified: a generalized herpetic infection (after the second and third courses, and therefore subsequent courses were delayed 1 month each), bacterial pharyngitis (during the third course), neuropathy, and the sensory-vegetative syndrome. On the background of the treatment, clinical-hematological remission was achieved. After five chemotherapy courses, the treatment was continued as monotherapy with rituximab (MabThera), 1 time in 2 months. At the beginning of the second course of rituximab (6 months after the end of the fifth course of PCT), cytotoxicity (up to 25 standards) was observed. The total bilirubin level increased up to 49.30 mmol/L and the content of gammaglutamyltranspeptidase, lactate dehydrogenase, and alkaline phosphatase rose to 451.80 U/L. The patient was hospitalized in the viral hepatitis clinic at the city hospital.

Clinical diagnosis: Chronic viral hepatitis B, HBsAg (+), with high viral load (HBV DNA, 33 million IU/mL). Chronic pyelonephritis. Cyst of the right kidney. Antiviral lamivudine therapy with virologic response, the 4th week (HBV DNA, 4,962 IU/ml). HHV-8-negative multicentric Castleman's disease, the plasma cell type. Condition after 4 courses of R-VCD therapy, a complete remission.

From anamnesis, we found that HBsAg was first identified on October 9, 2015. Previously, the patient had not been subjected to examination for markers of viral hepatitis. He denied alcohol intake, intravenous drug use, and a history of acute viral hepatitis in childhood. He received dental prosthetics in a private dental office in 2010. He was married; all members of the family were healthy and did not have hepatitis in anamnesis.

The physical examination revealed a severe general condition. Consciousness and orientation were normal. The findings on physical examination at admission were: height, 165cm; weight, 71kg; blood pressure, 95/70mmHg; heart rate, 85 beats per minute; respiratory rate, 18 breaths per minute; and body temperature, 36.8°C. The skin and sclera were pale, slightly icteric. The heart sounds were muffled. Auscultation of the lungs revealed vesicular breathing, which was weakened in the lower lung fields. The abdominal palpation revealed a slight pain in the right upper quadrant and a moderate hepatomegaly; ascites and lymph node enlargement were not observed.

Blood test: ESR, 47 mm/h; total protein, 69 g/L; albumin, 34.7 g/L; total bilirubin, 88.2 µmol/L; ALT, 794 IU/L; AST, 411 IU/L; ALP, 307 IU/L.

Enzyme immunoassay: Viral markers of HBV showed a positive HBsAg, antibodies to HBcAg were detected; anti-HCV antibodies were negative; ANA, positive; AMA, negative. Tumor marker results were as follows: AFP, 6.89 IU/mL; CEA, 5.66 ng/mL; CA 19-9, 5.97 U/mL.

PCR: HBV DNA, positive; viremia, 33,000,000 IU/mL

Abdominal sonography revealed a moderate hepatosplenomegaly; the structure of the liver was non-uniform and the diffuse changes of parenchyma were noted. During EGD, we identified varicose veins of the esophagus (degree I). Contrast-enhanced CT of the abdomen revealed diffuse changes in the liver parenchyma, calcification located in segment 7 of the liver, and perivesical effusion, cyst of the right kidney, and additional renal arteries of both kidneys.

Antiviral therapy with lamivudine (150 mg twice daily for 35 days) was conducted and showed improvement of the general condition, reduction of intoxication, and signs of liver failure. Viral load decreased to 4,962 IU/mL. The patient was discharged to outpatient treatment with a subsequent transition to entecavir therapy under the control of biochemical and virological parameters.

This example demonstrates the clinical manifestation of chronic HBV infection on the background of immunosuppressive therapy for Castleman's disease. In identifying anti-HBcAg, even in the absence of HBsAg prior to and during chemotherapy, it is necessary to determine the level of HBV-DNA every 1-3 months.^[17-20,35] Lamivudine has been used longer than other drugs in treatment for reactivation of HBV infection, but within three years of the application of this drug, resistance is developed in 53% to 76% of cases, which indicates the expedience of lamivudine therapy for a short course and at low level of viremia. Thus, a high viral load and the need for antiviral therapy for at least 12 months justified the switch to another drug in our case; the use of entecavir or tenofovir with a high barrier resistance was advisable. During

therapy, it is recommended to monitor the level of serum ALT (at least 1 time in 2 weeks for the first month of treatment, and then 1 time per month) and HBV DNA (during the 4th, 8th and 12th weeks from the start of antiviral therapy, and after that at least 1 time in 3 months on the background of therapy).

Conclusion

Since RS (Y) is a disadvantaged region with respect to the incidence of CHB, all patients with hematologic malignancies should be tested for serologic markers of viral hepatitis B and C before the start of chemotherapy. HBV seronegative patients should be vaccinated according to an accelerated vaccination schedule.

If anti-HBcAg or HBsAg is identified, viral load (HBV DNA) should be determined. However, regardless of the level of viremia, a pre-emptive treatment with nucleoside analogues is recommended. This therapy should be initiated prior to the appointment of chemotherapy, for the entire period of chemotherapy, and for 12 months after chemotherapy. In such cases, it is necessary to introduce algorithms to manage these patients, with compliance with continuity in the work of infectologists, oncologists and hematologists.

Competing interests

The authors declare that they have no competing interests.

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Reproductive Function in Patients with Non-functioning Pituitary Adenoma According to the Register of the Republic of Uzbekistan

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Abstract

The main aim of our study was to evaluate the reproductive system status and gonadotropic pituitary function in patients with non-functioning pituitary adenoma (NFPA) according to the register data.

Depending on the state of the reproductive system at the time of NFPA diagnosis, men and women can be classified into three groups: secondary hypogonadism (40.7%); normal state of the sexual system (22.0%); and PCOS in women (36.5%) and reduced testicular size in men (11.2%). Menstrual irregularities took place in 77.8% NFPA women of reproductive age (41.3% of them had galactorea-oligo/amenorrhea combined with moderate hyperprolactinemia), and sexual dysfunction occurred in 42.0% of male patients with NFPA. (*Int J Biomed.* 2016;6(2):133-135.).

Key Words: Non-functioning pituitary adenoma • hypopituitarism • reproductive function • gonadotropins

Introduction

The prevalence of pituitary adenoma (PA) is 80–100 cases per 100,000 of the population;^[1] endocrine-inactive or non-functioning pituitary adenoma (NFPA) accounts for 15%–30% of these.^[2-4] Annual incidence is 1 new case per 100,000 of the population.^[2] In contrast to hormone-secreting PAs, NFPA are not characterized by hormonal overproduction but usually present with symptoms and signs of tumor mass effects, such as visual field defects and hypopituitarism with growth hormone deficiency and disorders in sexual and reproductive function. hypopituitarism. At time of diagnosis of non-functioning pituitary macro-adenomas, 60 to 85% of patients present at least one pituitary deficiency, gonadotroph deficiency being the most prevalent (>80% of cases), followed by the somatotroph deficiency; thy-rotroph and corticotroph deficiencies are found in 20–50% of cases.^[1] Advances in immunoassays, immunohistochemistry, molecular biology

techniques and *in vitro* studies have allowed more detailed characterization of NFPA. Indeed, the majority of clinically NFPA can synthesize intact glycoprotein hormones and/or their free α - and β -subunits. Therefore, clinically NFPA can actually be considered a diverse group of tumors that also include, besides all these glycoprotein hormones, the null cell adenoma and oncocytoma.^[5,6]

According to the literature, more than 60% of patients with NFPA experience disorders in sexual and reproductive function,^[7,8] and their development is accompanied by a significant decrease in quality of life, which dictates the need for their active detection. Sexual dysfunctions are various: amenorrhea, menstrual disorders, decreased libido, impotence, and erectile dysfunction. These are often considered by urologists and gynecologists as manifestations of menopause, neurodistonia, and functional disorders associated with hormonal and endocrine-metabolic manifestations. We found that the development of hypogonadism and sexual dysfunction is observed not only with large adenomas, but also with microadenomas and after radiation therapy, all of which should be taken into account in the risk assessment.

The therapeutic options for NEPA patients are surgery, RT, medical therapy and conservative treatment. Individual

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factors, such as severity of symptoms (especially optic nerve compression) as well as tumor type and location, influence the choice of treatment. Small NFPA in asymptomatic patients do not require immediate intervention and can be observed.

The main aim of our study was to evaluate the reproductive system status and gonadotropic pituitary function in NEPA patients according to the register data.

Materials and Methods

The study was approved by the by Ethics Committee at the Republican Specialized Scientific-Practical Medical Center of Endocrinology. We analyzed the data of 325 NEPA patients (145 women and 180 men) aged from 18 to 70 years. Eleven men were over the age of 55 years. The mean age of women and men was 45.4 ± 13.9 years and 47.5 ± 11.7 years, respectively. Nineteen women were over the age of 50 years and 126 women were under the age of 50 years. Before diagnosis, duration of symptoms varied from 0.5 year to 6 years (mean duration 4.4 ± 2.6 years). All patients were evaluated by the same team of endocrinologists and operated on by the same neurosurgeon. All patients with NFPA underwent biochemical evaluation to confirm the diagnosis of hypopituitarism, radiological studies of sella turcica by X-ray, computerized tomography (CT) and/or MRI to analyze the mass (size, invasion, relation with optic chiasm) and assessment of visual field.

The main complaints at the time of the examination were visual defects, headache (81.2%), weight gain (36.4%), and sexual disorders. Among sexual disorders in women, we identified such abnormalities as opso- and polimenorrhea, amenorrhea, infertility, miscarriage, and uterine bleeding (69.8%), as well as different severity of galactorrhea (77.8%); in men we found decreased libido and potency (46.4%), decreased libido (18.9%), lack of libido (17.5%), infertility (32.3%), and gynecomastia (17.6%). Chiasmal syndrome in the form of optic nerve atrophy of different degrees and bi-temporal hemianopia was diagnosed in 163 patients (50.6%). Macroadenomas with extra-sellar expansion were present in the majority of patients at diagnosis, mainly as supra-sellar invasion.. After neurosurgical evaluation, a transsphenoidal pituitary surgery was performed in these cases.

All patients underwent either a gynecological or andrological examination, and women also underwent pelvic ultrasound. We determined the basal serum level of prolactin (PRL), growth hormone (GH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone in all patients, and estradiol and progesterone only in women. RIA was performed by using «Gamma -12» and «Strantg 300».

Statistical analysis of the survey data was performed using the software «Statistica 12.0» (Statsoft, Russia).

Results and Discussion

In 52(41.3%) women under the age of 50 years, we observed a reduction in levels of gonadotropins on the background of low serum estradiol level, which made it possible to diagnose the hypogonadotropic amenorrhea due to

tumor mass effect. Evaluation of the reproductive system state in 126 NFPA women under the age of 50 years allowed us to form the following groups of patients:

a) Group of oligomenorrhea (46/36.5%). Thirty-eight patients of this group had the clinical and biochemical features of polycystic ovary syndrome (PCOS) (polycystic ovaries during pelvic ultrasound examination, a high index of LH/FSH ratio, the elevated or subnormal concentrations of LH, and hypoplasia of the uterus in eight women).

b) Group of secondary amenorrhea (52/41.3%). Six patients of this group exhibited hypoplasia of ovaries and uterus during pelvic ultrasound examination; one woman had polycystic ovaries with low serum level of estradiol.

c) Group of preserved menstrual cycle and lack of pelvic change during pelvic ultrasound examination (28/22.2%). Three patients of this group had an increased serum level of estradiol and testosterone; one patient had hirsutism.

The LH/FSH ratio in patients with and without polycystic ovaries did not differ significantly: 2.7 ± 1.4 and 2.47 ± 1.3 , respectively. Ninety-eight (77.8%) women under the age of 50 years had galactorrhea (I and II degrees) in combination with oligo-amenorrhea and moderate hyperprolactinaemia. Fibrocystic mastopathy was identified in 17(13.5%) patients.

Evaluation of the reproductive system state in 169 NFPA men under the age of 55 years revealed the following results: 27(16.0%) men had high serum FSH level (norm: 1.3-11.5 IU/L), and 15 of them also had an elevated serum LH level (norm: 1.8-10.0 IU/L); 19 patients had a low testosterone level and hypopituitarism.

In 31(18.3%) men with low or normal LH levels, serum testosterone level was within the normal range. In 49(29.0%) men with low or normal LH level, the serum testosterone level was <11.0 nmol/l (norm: 10.4-41.6 nmol/L). Thus, secondary hypogonadism under the normal or decreased/increased levels of LH was diagnosed in 68(40.2%) NFPA male patients.

In 19(11.2%) men with low testosterone levels, testicles were hypoplastic; 25(14.8%) men experienced a marked reduction in secondary sexual characteristics. Seventy-one patients had sexual dysfunction, the most common being a decrease in libido. It has been previously established^[9] that libido weakening occurs with a decrease in the blood testosterone level below 5.0 nmol/L. A decreased libido took place in patients with normal serum testosterone level and at concentrations >5.0 nmol/L. All men with sexual dysfunction had elevated levels of PRL, which together with a reduction in testosterone level resulted in formation of this condition.

Thus, NFPA women under the age of 50 years may be represented by three groups, according to the state of reproductive system at the time of diagnosis: a) the normal state of the sex glands (22.2%); b) PCOS (36.5%); and c) hypogonadotropic hypogonadism (41.3%). The postmenopausal NFPA women can be divided into two groups: the normal state of the reproductive system (64.2%) and secondary hypogonadism (45.8%). In the presence of oligomenorrhea and PCOS, it is unclear whether pituitary adenoma or polycystic ovaries is primary. The combination of galactorrhea and amenorrhea, accompanied by hyperprolactinemia, often leads to overdiagnosis of prolactinoma.^[10] Women with amenorrhea

may have signs of hypogonadism (hypoplasia of the uterus and ovaries), ie, a secondary hypogonadism. Reasons for hyperandrogenaemia in 3 women without signs of PCOS are unclear. It is possible that there are some substances that are secreted by the pituitary tumor and lead to the development of hyperandrogenemia and polycystic ovaries in women, or the secreted gonadotropins have high biological activity that causes a similar clinical picture.

Clinically, male patients with NFPA fall into three groups, depending on the state of the reproductive system: a) normal state of gonads (48.6%), b) hypogonadotropic hypogonadism (40.2%), and c) reduced testicular size (11.2%). High blood concentrations of FSH in combination with an increase in volume of the testicles allows diagnosis of an active gonadotropin-secreting pituitary tumor. The development of secondary hypogonadism (low or normal levels of gonadotropins, decreased serum testosterone level and testicular hypoplasia) is likely due to the mechanical action of the tumor on adenohypophysis or effects of biologically modified hormones/substances secreted by the tumor.

Conclusions

Thus, according to the status of the reproductive system at the time of NFPA diagnosis, men and women can be classified into three groups: secondary hypogonadism (40.7%); normal state of the sexual system (22.0%); and PCOS in women (36.5%) and reduced testicular size in men (11.2%). Menstrual irregularities took place in 77.8% NFPA women of reproductive age (41.3% of them had galactorea-oligo/amenorrhea combined with moderate hyperprolactinemia), and sexual dysfunction occurred in 42.0% of male patients with NFPA.

Competing interests

The authors declare that they have no competing interests.

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Antioxidant Bio-Complexes from Renewable Arctic Raw Materials

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Abstract

We present the results of the investigation of the effect of mechanical activation on the content of low molecular weight antioxidants in powder mixture based on lichen thallus and small amounts of *Rhodiola rosea* to create nutritional supplements based on them. (Int J Biomed. 2016;6(2):136-137.).

Key Words: lichen thallus • *Rhodiola rosea* • mechanochemical activation • low molecular weight antioxidants

Introduction

Plants growing in harsh northern conditions attract considerable attention for the production of food additives able to enhance the body's immune system. These plants have to protect themselves from the extreme environmental conditions and therefore produce a range of protective substances including antioxidants.

The purpose of this study was to evaluate the effect of mechanical activation on the content of low molecular weight antioxidants in powder mixture of plant substances to create nutritional supplements based on them.

Materials and Methods

The object of the study was the physiologically active plant complex with a high level of adaptogenic action, which has been created in "Mechanical Biotechnologies" laboratory of the North-East Federal University. This plant complex is based on plant substances growing in Yakutia: the lichen thallus of *Cladonia rangiferina* (L.) ("Reindeer moss") and the rhizomes of *Rhodiola rosea* (Crassulaceae) in weight ratios of 5:1 and 10:1.

The manufacturing of such complexes includes the following operational stages: a) pre-grinding of raw materials

in a high speed mixer KSM-50 (South Korea), b) continuous mixing (for 5 hours) the crushed samples of lichen material and *Rhodiola rosea* in Lab Powder Mixer ("Junior" Italy), c) the joint mechanical-chemical activation in mechanical-chemical device (ZEM 7-80, Russia) without solvents in a single process step at a speed of 1200-1500 rev/min for 3.1 min.^[1]

Qualitative assessments of the flavonoid content were performed. The total amount of low molecular weight antioxidants (LMWA) was determined using the spectrophotometric method based on the capacity of iron (III) chloride to oxidize LMWA.^[2]

The studies were performed on eight samples in triplicate. Statistical data analysis was performed.

Results and Discussion

The multicomponent food additive includes the molecular complexes of lichen β -polysaccharides and bioactive substances (BAS) from roots and rhizomes of *Rhodiola rosea*: salidroside and flavonoid aromatic acids formed during mechanochemical activation of the above-mentioned mixture. Investigations with a 5% alcohol solution of AlCl₃ have showed that all samples have acquired yellow-green coloring caused by hydrogen bonds between carbonyl groups and hydroxyl groups, as well as the yellow-green fluorescence of the formed chelate complexes, that indicates the presence of flavonoids in the original samples. In a qualitative reaction with a 1% basic lead acetate solution, blue amorphous sediment has been formed, that is typical for anthocyanidins.

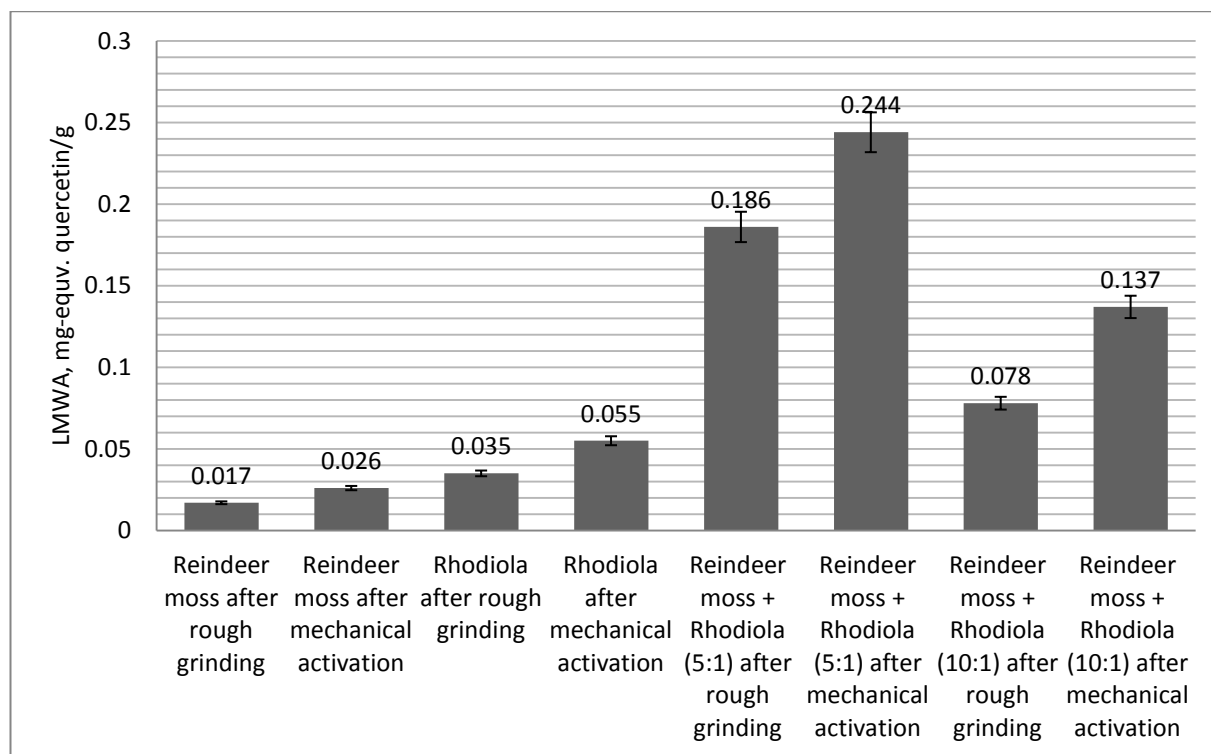


Fig. 1. Total amount of LMWA in the studied samples

The results of spectrophotometric studies indicated that the amount of low molecular weight antioxidants increases during mechanical activation of the raw materials, as well as with an increase in the proportion of the reindeer moss to *Rhodiola rosea* in the biocomplexes (Fig. 1).

Conclusion

The use of mechanochemical processing of the raw material destroys the cell walls, where the bulk of the biologically active substances (BAS) is contained, and, as a result, contributes to effective BAS release from the cells.

We have previously developed the new method to improve the quality and preservation of fresh liquid foods and bakery products by adding to their composition of mechanically activated powder mixture of lichen thallus *Cladonia P.* [3] Mechanically activated samples have greater bioavailability of biologically active substances, which greatly reduces the amount of food additives to 0.1-0.5% by weight of the finished product. Specification 9110-001-01727661-2012 was developed for making bread "Polarny". Bread "Polar" due to inclusion of bio-supplement "Yagel Detox" stays fresh for a long time, does not grow moldy and acquires special useful properties for human health: optimizes the immune system, increases resistance to viral and bacterial infections, and improves bowel function.

The developed bio-product based on the plant complex of lichen thallus *Cladonia rangiferina (L.)* and the rhizomes of *Rhodiola rosea (Crassulaceae)* with using mechanochemical biotechnology is supposed to use as a food additive in very small amounts (less than 0.5% by weight) to create liquid food products and bakery products having detoxifying properties and abilities to increase the adaptive potential of the human body, as well as the physical and mental capacity. The product may be useful for people having extreme professions, for persons with active lifestyle, people living in adverse environmental and climatic conditions, as well as for athletes in the period of intensive training and patients in the recovery period.

Competing interests

The authors declare that they have no competing interests.

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How Health Relationship Management Services (HRMS) Benefits the Elderly

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Abstract

Remote health monitoring and Health Relationship Management Services (HRMS) can provide health care solutions for the elderly, the fastest-growing segment of the U.S. population. The year 2030 *Problem* questions whether enough resources and an operative service system will be available fourteen years from now when the elderly population will be greater than what it is today. One solution for reducing elder health care costs is home care, which is a preferable alternative to institutionalization. Many elderly have access to health services or outreach medical care, but do not use them due to lack of accessibility to safe transportation. The elderly often have problems with medication misuse stemming from the aging process, such as loss of memory, poor vision, and fixed-incomes. Seniors have dietary problems that weaken immune systems, leading to dehydration and other health issues. They also experience depression and loneliness from living alone or even with family members. The elderly who experience these problems can benefit from Health Relationship Management Services (HRMS), a new healthcare paradigm using remote health monitoring in the home. (**Int J Biomed.** 2016;6(2):138-142.)

Key Words: remote health monitoring • health relationship management services • elder care • family care • 2030 problem

The initial wave of Baby Boomers turned 65 in 2010, making the elderly the fastest-growing segment of the U.S. population.^[1] A key public policy concern in the field of long-term care is the impending burden an aging society will impact the care-giving system and public finances.^[2] This is called the year 2030 *problem*, which questions whether enough resources and an operative service system will be available in 2030, fourteen years from now when the elderly population is greater than what it is today.^[2] This growth will be stimulated by Baby Boomers, who in the year “2030 will be aged 66 to 84—the ‘young old’— and will number 61 million people. In addition to the Baby Boomers, those born prior to 1946—the ‘oldest old’—will number 9 million people in 2030.”^[2] This population has a higher risk of dependency stemming from chronic conditions and will use up a disparate allocation of health care resources and dollars, both public and private.^[3] A recent study shows that the economic burden of elderly care by the year 2030 will require making changes now, before the day arrives when Baby Boomers start needing long-term care.^[2] This involves taking advantage of medical and behavioral health advances to allow seniors to remain as active and healthy as possible, and to change the cultural view

of growing old to ensure that all ages integrate into community life.^[2] One solution to these concerns is a new paradigm in health care called Health Relationship Management Services (HRMS)^[4] as it addresses problems associated with aging, living alone, and elder health risks, such as diet, dehydration, and medication misuse.

In the past decade, there have been many efforts to reduce health spending, yet the costs of health care continue to escalate.^[3] Medical innovations, such as cancer vaccines and prevention of Alzheimer’s disease, may result in better health and longer life,^[1] due to new medications and innovative surgical procedures that allow people to live longer. However, with age, many new health issues have arisen, such as the combination of physical symptoms, poor eyesight, minor safety hazards, medication management issues, social isolation, forgetting appointments, mental health, and poor nutrition or malnutrition, which can be alleviated by a new healthcare paradigm called Health Relationship Management Services (HRMS).^[5] ^[4] Coronary heart disease is the most prevalent condition that affects individuals 65 and older, followed by stroke, cancer, pneumonia, and the flu.^[5] Many seniors cope with heart conditions, such as coronary artery disease, high blood pressure, atherosclerosis, vascular disease, irregular heart rhythm, hypertension and congestive heart failure, as well as breathing problems and diabetes.^{[5][6]} Elders

also are prone to weakened immune systems, which leaves them open to opportunistic bacteria, viruses and diseases.^[5] Other physiological concerns include fever, water retention, swelling of legs, diabetic conditions, dehydration, diet, and improper nutrition.^[7] Maintenance of physiological health among the aging is important, not only for the individual, but also from reducing burdens on medical services.^[7]

Achieving and maintaining good nutrition is essential for elderly health and quality of life.^[8] At the root of dietary intake is availability, preparation and consumption of the proper quality and amount of foods, which may be impacted by several factors, to include social isolation and depression^[8]. Imbalances of necessary nutrients and energy gained from food increases the vulnerability of the elderly to unfavorable health outcomes, such as decreasing energy levels and chronic health complications, such as type 2 diabetes, high blood pressure, heart disease, stroke, and osteoporosis.^[9] Malnutrition often goes undiagnosed due to diet and inconsistent caloric, energy, taste and access needs.^[9] Diet imbalances also can lead to lengthier hospital stays and possibility of readmission, physical, and cognitive function impairment.^[8]

Seniors sometimes have difficulty recognizing bitter and salty tastes, which result in an increase in salt intake in the diet, which can lead to high blood pressure.^[9] Also, many elderly retain their capacity to appreciate sweet tastes, thus consume too many sugary snacks, beverages or desserts, which cause weight gain due to a slowing of metabolisms.^[9] Nutrition and reduced metabolisms are directly related to both weight loss and weight gain in the elderly.^[9] Moreover, the elderly, especially those suffering from chronic conditions, sometimes have less energy.^[9] Thus, reduced activity can lead to obesity.^[9] Conversely, limited food access, a decrease in appetite, side-effects from medication, in addition to medical problems can create weight loss.^[9] Also, seniors tend to not purchase the foods that are rich in vitamins and minerals, due to fixed incomes or outright poverty.^[9]

A common problem among the elderly is dehydration because: (1) they have a limited capacity to conserve water, (2) are not aware of their thirst, and (3) often avoid drinking fluids due to overactive bladder problems.^[9] Furthermore, the elderly are more apt to lack proper hydration during illness and in warm-weather months.^[9] Dehydration is also caused by medications and chronic medical conditions.^[9] Mild dehydration symptoms include constipation, headache, dizziness, low blood pressure, rapid heartbeat, and loss of consciousness, while more severe complications include seizures, kidney failure, swelling of the brain, heat injury, and death.^[9]

Almost 90% of individuals over the age of 65 wish to live at home for as long as they can because staying in familiar surroundings offers emotional well-being.^[10] However, studies indicate that a high number of elderly who really ought to be in an assisted living care facility still live at home, and often live alone.^[10] No matter the severity of a disability or dependence, elders are encouraged to be independent at home rather than being institutionalized. There are problems associated with such an arrangement aside from health problems, among which are medication, transportation issues, depression, and

loneliness. For the elderly who live at home, medication can either be a health lifeline, or it can be a calamity waiting to happen.^[11] Problems with medication are very common, and deadly results can occur if too much medication is taken or if doses are missed.^[11] There are many reasons why the elderly do not take their medications properly. Misuse of pills often occurs with seniors who have vision problems and cannot read small print on labels.^[11] Memory loss for elderly suffering from Alzheimer's disease or dementia may forget to take their medication or cause an overdose when they cannot remember whether they took their medication already. Also, seniors on fixed incomes, or are low-income, may cut back on the prescribed dose by cutting their pills in half or simply take no medication for long periods of time.^[11] Elderly persons with hearing loss may not be able to hear the doctor or pharmacist's instructions.^[11] For seniors who have trouble swallowing a capsule or tablet, they tend to crush or break them, or mix the medication in with their food, but some long-acting medications may be released too fast, or won't work as intended and could cause sickness.^[11]

Most elderly individuals prefer self-sufficiency and would prefer to depend on their family as principal caretakers only in times of need which can take place in the home by family or caregivers.^[12] The family is, and has been, the primary means of elderly care and assistance in which elders are allowed to live at home in familiar surroundings. Family support is one social network that positively affects an elderly person's self-image, sense of importance, and feelings of being loved and respected. Home-care services provide quality of life services, such as personal care, housework assistance and help with daily tasks. Whether home care or day care, such services contribute to a sense of security and well-being, and prevent feelings of social detachment.^[13] These alternatives to institutionalizing the elderly contribute to better physical and mental capacities since elders can participate in decision-making, maintain their home life, have a sense of control over their lives, and establish social ties.^[13]

Not all elderly, however, are fortunate enough to have family or day care. Some elderly persons have a negative day-to-day existence due to lack of income, poor health, lack of accessible and safe transportation, fear of being a crime victim, loneliness, social isolation, and limited family contact.^[11] Although they are eligible for health services and outreach medical care programs, many elderly people do not use them due to a lack of knowledge about how to access these services and restricted mobility because they cannot reciprocate transportation favors provided by friends or families. Community-based transportation services for seniors often require advance approval and arrangements.^[11,14-17] Urban medical care is often avoided due to lack of safe accessible public transportation.^[11] ^[18] Many elderly people are justifiably fearful of becoming crime victims while using public transportation.^[11,19,20]

A recent Dutch study suggests that loneliness is a risk factor for the dementia.^[21] The study's findings suggest that feelings of loneliness contribute independently to the risk of dementia in later life. Individuals who feel lonely in old age are much more prone to develop dementia than those who do

not feel lonely. People suffering from loneliness have a 64% greater risk of dementia, but this risk is dependent upon having those feelings and not simply because someone lives alone or is socially isolated, unmarried, or without social support.^[21] Additional risks for the elderly are Alzheimer's disease and other dementias that may be caused by other conditions that include depression and mild cognitive impairment.

Solutions

Homecare telemedicine for geriatric disease management is being used for many medical illnesses, such as chronic conditions and heart disease. Home telemonitoring of elderly patients with congestive heart failure confirmed a reduction of the rehospitalization rate and an improved monitoring of drug consumption by the patients.^[22] Makers of remote monitoring technology solutions for senior care empower providers to proactively provide the utmost quality care possible by gathering critical health information. Hospitals, doctor's offices, home healthcare facilities, and nursing homes are embracing wireless remote monitoring devices to communicate patient data.^[23] When equipped with the right information at the right time, caregivers now can reduce costs and increase senior independence.^[24]

Telemedicine technologies can help seniors face challenges linked to social connectivity, emotional health and cognitive and physical ability.^[25] Since many seniors want to live in their homes for as long as they can, technology, such as prosthetics, wearable sensors, and other tools for daily living make it feasible.^[25] New technology is making it a possibility for adult children to monitor the activities and routines of their aging parents every day, making it possible for seniors to live in their homes rather than being transferred into an assisted living facility.^[25]

The risk of seniors of being socially isolated or lonely is increasing, possibly due to living alone, retirement, poor health, and death of friends and family members.^[26] Research shows that remote monitoring shows promise for geriatric depression, and has become a key factor in helping the elderly and chronically ill live independently and safely in their homes while reducing health care costs.^[24] Many of the problems associated with long-term elder care now and in the future can be addressed by a new healthcare paradigm called Health Relationship Management Services (HRMS).^[4]

Health Relationship Management Services (HRMS) Solutions

Health Relationship Management Services (HRMS) as a solution allows the elderly to self-monitor in the safety of their own homes, thus diminishing doctor's visits, which will eliminate fears of reliance on public transportation, becoming crime victims at bus stops, or being injured while entering or exiting their own homes. Medication misuse that often leads to severe consequences can be monitored remotely, allowing advocates to step in and correct it. Essential nutrient imbalances gained from food that increases the elderly vulnerability to undesirable health outcomes can be minimized, since diet,

dehydration, nutrition and dietary intake can be tracked and intervention can take place if problems arise. Seniors' independence and self-sufficiency increases, since they have empowerment over their own healthcare.

HRMS supports the diverse and changing needs of the elderly by empowering them to take control of their own health.^[4,27] HRMS can lead to lower medical costs for hospital and doctor's visits, allowing the elderly to remain independent in their own homes. An online patient portal app connects patients to the outside world to minimize isolation and loneliness. HRMS is designed to monitor an individual's health daily to detect changes in health data that would require immediate attention. New remote health care monitoring technology and HRMS is a solution to these rising health care costs, transportation worries, isolation, and barriers to health care access.^[4] HRMS can help allay those feelings by providing elderly individuals with a sense of belonging to a supportive health community in which someone is watching over them every minute of every day and monitoring their health.^[4]

Case Study: Walter

Walter is an 85-year-old diabetic widower with a history of heart disease who is being discharged from the hospital after treatment for pneumonia. He is being sent home without the benefit of a full-time caregiver since his family lives out of state. Walter has been taking four prescription medications during his hospital stay and has been prescribed two new medications at discharge to take when he gets home. His primary care provider has scheduled a follow-up appointment for two weeks after discharge. Although a hired caregiver will stop in each day for a few hours to prepare his meals, administer medication, and assist with bathing, Walter will be essentially alone once he goes home. Even though Walter still has his driver's license, his sight is failing and he doesn't feel confident to drive his car more than a few blocks to the store for groceries. Thus, he has no reliable transportation to get to his doctor's appointments across town, except for his neighbor Mrs. Conner who has offered to take him.^[28]

At the hospital, Walter gets his discharge papers from a nurse, which he has trouble reading due to failing eyesight in spite of having eyeglasses. He is taken down to the hospital pharmacy to pick up his prescription medication. His neighbor, Mrs. Connor, has arranged to meet him there and then drive him home. At the pharmacy, Walter is given the remote Health Relationship Management System (HRMS) health monitoring system that his physician prescribed for him. The pharmacist explains to both Walter and Mrs. Connor how the system works, so they both clearly understand the procedure. He also provides Walter with his other prescription medications along with a lengthy set of instructions for their use. Due to his age, Walter feels overwhelmed by the complex instructions for his medication use, as there are so many pills that must be taken at different times of the day.

With the help of Mrs. Conner, Walter arrives home and gets settled in. Before she leaves, Mrs. Connor helps Walter set up his HRMS monitoring system by creating a profile on the

downloaded app on Walter's smartphone and logs in according to the enclosed directions. At this point, Walter is prepared to use the health monitoring system every morning and evening, so it can read his personal health data. Mrs. Conner tells Walter that she will visit him whenever she can, and leaves her phone number for Walter to call if there is anything he needs or if there is an emergency. More importantly, in Mrs. Connor's absence, the HRMS system will monitor Walter's medication to prevent errors and provide him with an online connection to a caring health community.

Soon after Mrs. Connor leaves, Walter starts flicking through the health app screens on his phone, and notices that there is an interactive online magazine that looks interesting. He reads stories of people who have experienced health issues and becomes engaged in them by interacting with the authors. There are health inspired games that he likes, too, that offer points as a reward that can be cashed in for gifts. He also has an interest in health matters and enjoys reading short paragraphs about various health conditions on the app to get up-to-date information on new procedures, symptoms, or health risks.

All is well with Walter for the next few days, but since his real-time health data has been captured daily using HRMS, sudden inactivity with the system has been detected. HRMS tracks medication and has an escalation path through the system that indicates when immediate action must be taken.^[29] The Communication Center advocate calls to check in with Walter to take appropriate action. There is no answer, so the advocate calls Mrs. Connor and asks her to go visit Walter right away. She finds that he has not taken his medication because he misplaced his glasses and could not read the labels on the pill bottles. He is at risk for recurring pneumonia, but fortunately, because Mrs. Conner has been advised to visit Walter, he receives the proper attention, takes his medication, and avoids a trip to the ER for readmission to the hospital.

A few months have passed, and due to his age, Walter's children have gotten his driver's license suspended because of his failing eyesight, so he can no longer drive. Up until now, Walter actually liked living alone independently and has not felt lonely because he relished his independence, as being alone and feeling lonely are not the same.^[30] Now without the license to drive, the lack of independence and freedom has intensified Walter's sense of isolation, and he aches for social contact. Feeling lonely with the perceived absence of social attachments increases the risk of cognitive decline and is associated with the onset of dementia. With HRMS, Walter's contact to the outside world consists of watching television, speaking to some friends occasionally on the phone, and visits from Mrs. Connor. More importantly, Walter is also connected to a caring healthcare community through HRMS that gives him the confidence that there is someone who cares about him and is watching over him, albeit remotely. By connecting to HRMS, Walter's sense of loneliness has abated, and he continues to live happily by himself independently in his own home.

With the introduction of new technology that helps seniors live safely and productively in their own homes, a story like Walter's could really happen. HRMS is a new

healthcare paradigm that is designed to help seniors who are living at home, either with caregivers or by themselves to avoid some of the problems associated with aging. Remote health monitoring and HRMS will be able to provide elderly persons with independence and control over their health issues. For elderly individuals who either live alone or stay with family, HRMS will one day reduce medical visits and associated difficulties with transportation. From the online patient platform, patients' feelings of isolation and loneliness will be assuaged by the knowledge that someone is looking out for their health and that they are part of a caring health community.

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How Health Relationship Management Services (HRMS) Benefits Corporate Wellness

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Abstract

The typical worker spends about 47 hours a week commuting sitting in cars, trains, buses, or sitting at their desks. These statistics show that maintaining a healthy work and life balance has become progressively important. Workplace wellness and health promotion are of central importance for any organization in today's world. People are becoming highly conscious about their health and seek to ensure that they are provided with best medical services and facilities in case of any health issue. Organizations have switched to proactive strategies for the healthcare of their employees. Billions of dollars are spent on the workforce only after illnesses or injuries have occurred. Over the past several decades, healthcare services have drastically changed, altering the manner in which healthcare was previously managed. Technological advancements in medical systems have revolutionized the healthcare industry, and digital health tracking has been quite successful in monitoring patients' health. Since patients are continuously monitored, no matter where they are, these systems can indicate patients' adherence to medical protocols and act as a warning sign for such diseases as heart problems, Alzheimer's disease, and many others. Health Relationship Management Services (HRMS) is a new paradigm which defines comprehensive healthcare for an individual. HRMS is a complete health ecosystem suitable for the workplace, which enables healthcare providers to collect personal health data from various sources, analyze it for positive outcomes, and take action to preserve an employee's good health to reduce absenteeism or turnover. HRMS can act as a preventative sentinel for corporate well-being as well. (**Int J Biomed. 2016;6(2):143-145.**)

Key Words: corporate wellness • health relationship management services • patient health data • lifestyle

Many employees spend more hours at their workplace than anywhere else, not to mention the time spent commuting. The typical worker spends about 47 hours a week in these activities,^[1] many of them sitting in cars, trains, buses, or at their desks. A recent study found that a person who spends long hours sitting down each day, has a higher risk of premature death, even if he or she engages in regular daily exercise.^[2] Urban environments often require behavior that requires sitting down: commuting, in the workplace, or even during time spent at leisure, such as watching television or movies. These statistics show that maintaining a healthy work and life balance has become progressively important.^[2]

Traditional corporate wellness programs encourage employees to stop smoking, lose weight, or get more exercise, with the goal of decreasing the company's overall healthcare costs by having healthier employees. However, such programs have not always met those goals, as research shows that cost increases have either stayed steady or even

increased.^[1] Wellness is not merely the absence of illness, but also includes the concept of total well-being of the individual embodying social, spiritual, emotional and intellectual health, to include physical health. It also encompasses a lifestyle of healthy behavior and healthy environments that are supportive not only at work, but also in the home and community.^[3] Thus, many organizations are turning toward promoting a healthier work environment and health promotion policies for their employees. Corporate wellness programs are effective ways to establish this balance. Programs emphasizing corporate wellness benefits can be instituted in several ways. One new health paradigm that is providing a total health ecosystem is Health Relationship Management Services (HRMS)^[4] that combines remote health monitoring that captures individual health data, sends it to the cloud for restructuring into actionable information that can be used to anticipate changes in health and allow access for caregivers to provide solutions or treatment. HRMS allows individuals to engage in their own healthcare and encourages lifestyle changes for better well-being. The common goal for all corporate wellness programs is to promote employee, employer, and organizational well-being.

Employees who do not have the opportunity to engage in corporate wellness programs may be susceptible to serious illnesses, which may lead to long-term disability or discontinuing their employment. A primary benefit of corporate wellness is reducing rates of injuries and illnesses among workers, since many employees experience work-related injuries as well as development of health complications such as heart disease, diabetes, or stroke.^[2] Prevention of employee illness can also lead to reducing employee absenteeism, since people who are unhealthy, stressed, or overworked have a tendency to experience illness more so than employees who are healthy.^[2] Programs focusing on corporate wellness benefits can drastically reduce these problems. As an example, Coors Brewing Company decreased employee absenteeism 18 percent after introducing a corporate wellness program.^[2] Coca-Cola saved \$500 per employee yearly, even though only 60% of its employees participated in a corporate wellness program.^[2] Also, retention of key employees is enhanced, leading to less turnover.

Corporate wellness is also the process of enabling employees to control and improve their own health. On average, half of an employee's waking hours are spent on the worksite, resulting in stress and lack of physical activity that constitutes health problems. Many organizations have developed strategies to align their goals and objectives to bring about the sustained performance of business by having effective relationships with their employees. One such strategy is the implementation of Health Relationship Management Services (HRMS),^[4] which is a health ecosystem that continuously monitors an employee's health data for prevention and/or treatment.

As an example, Zappos, an online e-business selling shoes, clothing and many other products to its customers, has rapidly expanded its operations over a short period of time because of successful implementation of a similar method as HRMS.^[4] Zappos is admired for its employee wellness programs and healthy environment.^[5] Zappos' workplace is an efficient LEED certified building constructed for the benefit of Zappos employees. This has made the workplace a happier, healthier, and more productive milieu for employees, which translates into happier customer service and customers.^[6]

New healthcare technologies can now monitor an individual's personal health data continuously with services that provide health alerts when the data deviates from a healthy pattern. Such technologies can engage an employee in his/her own health care and encourage a healthy lifestyle. Health Relationship Management Services (HRMS)^[4] is such a system that is ideal for employee wellness as it makes it fun and engaging for individuals. Instead of adhering to traditional approaches and methodologies for employee wellness, Zappos focused on making its employees happy by encouraging them to participate in an environment that encourages healthy activities and programs. Zappos believed that motivation is the key to success and values its employees' feelings and their viewpoints, rather than forcing rigid and overly-planned corporate goals on them.^[9]

Healthcare services have drastically changed over the past few decades, and the technological advancements in

medical systems have revolutionized the healthcare industry. Zappos took the risk of incorporating such new systems of healthcare, which has definitely paid off for the company and employees since most employees now love working there.^[6] One such similar paradigm is HRMS in which individuals can engage in their own healthcare and lifestyle changes. Along the principles of this new paradigm, Zappos promotes fitness by monitoring employee health, providing a health station so employees can check their blood pressure, weigh in, and receive a body fat percentage reading. Employees can also log their fitness activities to earn rewards for their physical activity. Zappos also offers free on-site fitness classes and boot camp-style training.^[9] Employees can participate in endurance events, such as 5Ks and marathons, and if they finish the race, they are rewarded by being reimbursed for their entry fees.^[9] All of these activities are similar to the HRMS paradigm that engages individuals to improve their own healthcare and observe wellness. Employees at another company, VISTA Staffing Solutions, spend on average 10-12 hours a day sitting. The company decided that its previous wellness programs did not work, so they switched to "stand-up desks, wireless head sets and walking treadmills" to create a healthier work environment.^[2] The goal was to promote healthy eating habits and weight loss to boost employee productivity.

Research has shown a link between employee nutrition and exercise and how it affects their overall productivity.^[7] Obesity and related diseases, have led to a significant increase in healthcare costs for many organizations. Zappos was aware that obesity is one of the largest contributors to health problems linked to diseases such as diabetes, hypertension, cardiovascular disease, and cancers. Moreover, these health problems resulted in lower employee productivity, higher absenteeism and an increase in employee turnover. Additional costs aside from medical claims occur when employees are not performing at optimal level. Technological systems can indicate patients' adherence to medical protocols and acts as a warning sign in many cases such as hypertension, cardiac disease, and many other diseases, as patients are continuously monitored no matter where they are.

Giving attention to overall employee wellness, Zappos designed policies to facilitate employee health by offering healthy food options and allowing for exercise time. Zappos focused on employees' happiness by encouraging them to engage in a flexible, fun approach to wellness, such as Wellness Adventures, March Madness, and Recess Tuesdays, that recruits employees from different departments and encourages them to mix and have fun away from work, doing such activities as laser tag, playing basketball or jumping on a trampoline.^[6] To encourage participation, there are incentives to wellness events. By using a similar concept as HRMS, Zappos can monitor the employees' health records through online portals and can determine whether its employees are following healthy lifestyles and are getting proper healthcare. This is why there is an increased need for employee wellness programs, and systems, such as HRMS, are becoming fundamental to many businesses such as Zappos.

Zappos considered how responsibility for action on health determinants and health behaviors was balanced

between employers and employees. The development of systems, such as HRMS, promotes and fosters health and well-being of individuals, corporations, and communities. HRMS helps to develop plans to increase physical activities and increase awareness of health problems and education. Furthermore, applications and services which use the internet as a platform have allowed gathering and sharing of medical, health, clinical records and data that can be analyzed, stored, and made easily available to different participants in the healthcare system.^[10] This will encourage employees to willingly provide personal health data that will result in job satisfaction, as satisfied employees are more likely to contribute as a consequence of increased duty, responsibility and obligation to employers. Zappos has adopted employee wellness strategies and found that its employees performed better than before as they are more confident, fresh and active while performing their jobs.^[6] Zappos wellness coordinator Kelly Maher has remarked that it is all about encouraging people to engage in wellness voluntarily, not by force. Programs that are successful are ones that engage team members to become energized on their own.^[2] HRMS can act as a preventative sentinel for corporate well-being as well.

Conclusion

Zappo's, Coors Brewing Company, Coca-Cola, and VISTA created a unique wellness program to engage employees in unique health-through-fun health activities, as well as healthy workplace environments. Benefits of corporate wellness combined with the benefits of HRMS can lead to happier, healthier employees who like their working environment. Companies should take advantage of corporate wellness and HRMS benefits to avoid stressed, sick, or unhappy employees who experience illness, absenteeism, injuries and increased healthcare costs. Instead, companies can experience an increase in employee productivity and retention. A monitoring system, such as HRMS, can standardize patient health data, and continuously follow-up with relevant feedback to actionable data. Therefore, as companies adopt HRMS, health-related costs may decrease while providing better quality services to employees who can receive health services

as a product.^[11] A harmonious, healthy workplace provides all employees with the benefits of corporate wellness.

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How Health Relationship Management Services (HRMS) Benefits Telemedicine

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Abstract

Yousef lives in a remote area of Pakistan with limited access to healthcare. As a result of not having proper diagnoses, care or medication, Yousef's hypertension has begun to damage his heart. A major barrier for Yousef getting good healthcare is the long distance between the village and quality care hospitals that are miles away, so he becomes a patient at the local village quack clinic that is not qualified to treat Yousef's complicated health condition. Telemedicine in the form of Health Relationship Management Services (HRMS) has come to the village, so now, Yousef can receive proper diagnoses, advice, medication and treatment without having to travel afar. Telemedicine allows specialists that are miles away to access Yousef's personal health data to make meaningful decisions about his healthcare. (*Int J Biomed.* 2016;6(2):146-147.).

Key Words: telemedicine • health relationship management services • health condition • healthcare

Yousef is a 60-year old man living in a very small village in the Baluchistan province of Pakistan known as *Sofia*. He is the only income provider for his family of a wife and two daughters. Yousef has been suffering from hypertension for many years, but he has never been able to get the proper treatment for it due to living in the remote mountainous region in Pakistan. The health services in *Sofia* are low-quality, while quality health services are located in the nearest city almost 100 km away. Initially, Yousef went to the local health clinic to cure his hypertension because he lacked transportation and could not afford the quality care in distant healthcare facilities. Unfortunately, the clinic was staffed by untrained and under-experienced people. As a result of receiving erroneous healthcare in his village, Yousef's health was seriously damaged and propelled his hypertension into a full-blown heart problem. Yousef did finally visit the nearest government hospital, but he was told that the hospital was not equipped with the necessary technology or health specialists needed to deal with his acute health condition. Yousef was told that he needed further assessment by a heart specialist, but the nearest one was inaccessible due to the remoteness of the village. Soon, his daughters heard that there was something new being introduced in their village clinic that could help their beloved father. They were informed that the clinic was incorporating Health Relationship Management Services (HRMS), which is

an advanced form of telemedicine services.^[1,2] Yousef's main barrier that has kept him from getting appropriate quality healthcare is the long distance between his village and good hospitals and qualified specialists. Now, with telemedicine, Yousef can get expert long-distance advice from professionals who can recommend the proper treatment for his condition.

Now that Yousef's issue is resolved, he no longer needs to travel a long way to the main city for health services. With quality healthcare so close to home, Yousef is able to visit the local hospital for HRMS to care for his condition. A care specialist is assigned to Yousef's case for diagnosis and treatment through telemedicine, which offers medical services to remote locations. After having the proper professional medical care, Yousef is now experiencing a different lifestyle. Through the use of a health monitoring system that captures his personal health data, Yousef now can immediately know the result of his health metrics. Yousef's health data is collected daily and stored in the cloud where it is restructured by analytics software for evaluation. This analyzed data, in an aggregated form, is represented by an individualized health scoring and demographic grading system. The meaningful data is analyzed by the heart specialist who monitors Yousef's health condition. In essence, the health data captured by the system each day is measured against Yousef's health database, and if a change should occur, his care-provider is immediately alerted and can now access his health information in order to recommend treatment and lifestyle changes for optimum health. The care specialist discussed Yousef's case with physicians at

the provincial hospital many miles away, who then diagnosed Yousef with chronic hypertension and diabetes. As a result, the care specialist has prescribed a different course of treatment plan for Yousef. Now, Yousef and his family are very satisfied with HRMS benefits he receives at the local clinic. Yousef's daughters are relieved that their father's life is in safe hands, and are pleased that they can now communicate with the specialist remotely, due to availability of the telemedicine treatment.

The stigma that was once associated with the rural areas that lacked quality health services are just a dim memory, and the dream of quality healthcare in remote areas is now a reality. At the outset, Yousef and his family were given the basic information about HRMS: what it consists of, and every step that is involved. It was very comforting for the family to know the status of Yousef's condition immediately in their own home without having to travel 100 km for the treatment. It was very educational and a relief for the family to know that solutions to many chronic medical health conditions are now available to them in their own locale. Now, the last step is to continue using the system for continuous monitoring of Yousef's health condition. This is the real benefit of this advanced telemedicine service. Day-by-day, Yousef's health has improved; he started taking his prescribed medications on a regular basis to treat his chronic condition. The results are apparent, and he has resumed his business in his village. The medical care that once was out of reach to remote villagers like Yousef is now within reach.^[3]

Yousef's family was astonished at how a physician a hundred miles away could prove to be so helpful by connecting to a telemedicine system in their own village. They spread awareness to the other villagers, so that they, too, can also improve their health and their relatives simply

just by availing the services of HRMS. As a result, the local villagers patronize the local hospital where the HRMS system was put in place by health officials. In turn, many people have been diagnosed with chronic conditions that were once misdiagnosed by the unexperienced set of so-called doctors in the village. Telemedicine made such a positive impact on the inhabitants in the village, that it is a widely-accepted fact that the HRMS benefits are effective. Patients can be in touch with any specialist thousands of miles away, while in their own homes or village. Health Relationship Management Services helped Yousef and his local villagers by resolving their health problems.^[4] Yousef's story, and others like his, could be made possible in actuality with the advent of advanced telemedicine devices and Health Relationship Management Services (HRMS).

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