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INNOVATION IN DIAGNOSTIK UND THERAPIE DES PARKINSON-SYNDROMS

Dr. Med. Wolfgang Fisher

Neurologische Kliniken Beelitz - Heilstätten, Deutschland

Zusammenfassung

Die Erkrankung ist nach ihrem Erstveröffentlicher, James Parkinson 1817 (*An essay on shaking palsy*), Medizinhistorisch betrachtet finden sich aber bereits um 1500 Symptombeschreibung dieser Erkrankung bei Leonardo da Vinci. Seit 1817 bis in die Neuzeit entwickelte sich eine rege Ursachenforschungstätigkeit im Rahmen der Parkinson-Erkrankung. Berühmte Namen wie Charcot, Tretjakow, Carlson und Davis haben an der Erforschung dieser Erkrankung mitgewirkt.

Im Rahmen der Entwicklung therapeutischer Zugänge gelang mit der Einführung erster synthetischer Anticholinergika ein gewisser spezifischer Therapieansatz. Ab 1961 wurde L-Dopa in der Klinik eingesetzt. Diese Therapie wurde von Birkmayer und Hornykiewicz begründet. Später kamen Modifikationen dieser Behandlung und die Einführung der Amantadine, Schwab 1969, hinzu. In der Folgezeit gelang 1974 Calne die Einführung der Dopaminagonisten und ab 1975 etwa wurden MAO-B-Hemmer und COMT-Hemmer mit in die nunmehr umfangreichen Therapieoptionen eingebaut.

Seit 1954 gab es erste operative Behandlungsansätze im Sinne stereotaktischer Nukleotomien zur Behandlung des pharmakotherapie-resistenten Tremors, und im Rahmen der Weiterentwicklung der operativen Methoden wurden Transplantationen von embryonalem Gewebe und Implantation dopaminergischer Epithelzellen aus der Retina mit wenig klinischem Erfolg getestet. Die Einführung der stereotaktischen Tiefenhirnstimulation begründete dann den Erfolg der operativ-therapeutischen Optionen bei Morbus Parkinson und anderen extrapyramidal-motorischen Erkrankungen.

Die Herausforderungen bei der optimalen Patientenbetreuung sind die verschiedenen Stadien der Erkrankung, wobei im Frühstadium diagnostische Probleme, die Auswahl der optimalen Therapie und die Frage nach neuroprotektiven Ansätzen die Hauptinhalte sind.

Im mittleren Stadium der Erkrankung ist der therapeutische Zugang dadurch gekennzeichnet, dass die L-Dopa-Wirkung scheinbar nachlässt und dass das



Oberarzt Neurologie,
Universitätsdozent Sozialmedizin
Katholische Universität Eichstätt
Fischer2@rehaklinik-beelitz.de

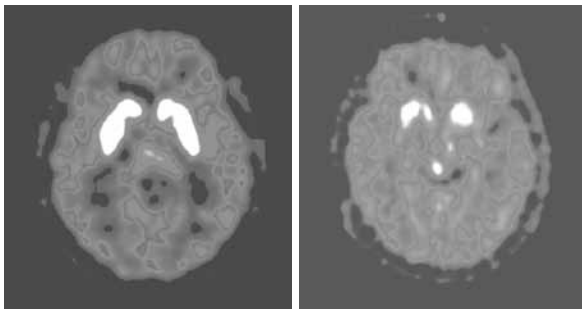
therapeutische Fenster durch das Fortschreiten der Neuronendegeneration zunehmend eingeengt wird.

Im Spätstadium werden die therapeutischen Prozeduren durch die allgemeine Verschlechterung des klinischen Zustandes des Patienten und durch das L-Dopa-Spättsyndrom und weitere Nebenwirkungen determiniert. Hier haben sich in den letzten Jahren im Rahmen der Therapie, aber auch im Rahmen der diagnostischen Treffsicherheit eine Menge an Neuerungen ergeben, die wie folgt zusammengefasst werden können:

In der Diagnostik gibt es mittlerweile spezifische nuklearmedizinische Methoden, die zunehmend in die Standarddiagnostik mit eingehen, wie z.B. Spect, PET und DAT-Scan.

In den letzten Jahren wurde die Hirnsonografie zu einem diagnostischen Verfahren entwickelt, das in den Händen des geübten Anwenders immerhin eine diagnostische Treffsicherheit von über 70% erreicht.

Hinsichtlich der therapeutischen Optionen besteht Einigkeit darüber, dass die tonische Rezeptorstimulation des D2- und D3-Rezeptors am postsynaptischen Ende im Corpus striatum die effizienteste Methode ist um das L-Dopa-Spättsyndrom erfolgreich zu verhindern und Folgen zu minimieren, insbesondere Glättung der Fluktuationen. Hier hat sich im Rahmen der L-Dopa-Applikation die tonische Rezeptorstimulation im Form der Duodopa-Pumpe als kontinuierliche enterale Gabe einer definierten L-Dopa-Menge über den Tag verteilt etabliert. Auch die Dopaminagonisten-Applikation konnte in Form der Apomorphin subcutan- Dauerinfusion (Apomorphinpumpe) im Rahmen der tonischen Rezeptorstimulation etabliert werden.



PET beim Gesunden

PET bei M. Parkinson

Als dritte Säule der Dopaminagonisten-Applikation im Sinne einer tonischen Rezeptorstimulation ist die Form der transdermalen Applikation von Rotigotin in Form eines Pflasters (Neupro- Pflaster). Wenn bei den sehr invasiven Verfahren der Duodopa-Pumpe und der Apomorphin subcutan-Infusion ein hohes Maß an kognitiven Fähigkeiten beim betroffenen Patienten vorhanden sein müssen, bzw. in seinem sozialen Umfeld geschulte Mitmenschen diese Aufgabe überwachen, ist die Anwendung des Neupro-Pflasters, also der transdermalen Agonisten-Applikation relativ problemlos und hat zudem den Vorteil, das dieses Verfahren auch bei schluckgestörten Parkinson-Patienten zur Anwendung kommen kann.

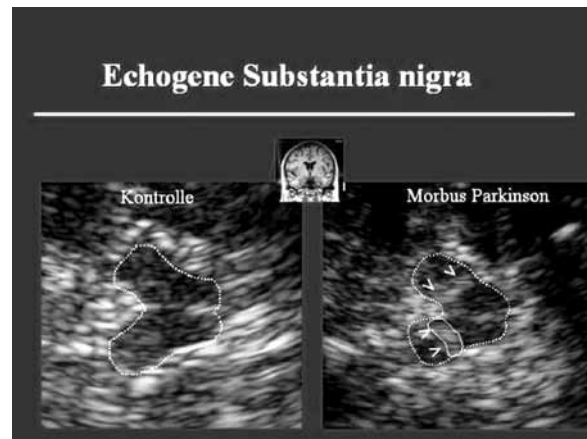
Bezüglich der chirurgischen Therapieoption hat sich die selektive Tiefenhirnstimulation an verschiedenen Zielorten des Mittelhirns etabliert. Hier ist es möglich geworden, bestimmte Zielsymptome selektiv positiv mit Medikamenteneispareffekt zu beeinflussen.

Neben diesen Fortschritten in der Parkinson-Diagnostik und -Therapie bleiben nach wie vor noch offene Fragen. Insbesondere befasst sich die aktuelle Parkinsonforschung mit der Frage, ob Morbus Parkinson eine Erbkrankheit ist, da in 10 bis 15% der Fälle weitere Familienmitglieder krank sind. Zumindest besteht nach heutigem Erkenntnisstand eine genetische Determination an diese Erkrankung zu erkranken.

Eine weitere Frage, ist die Frage nach den Ursachen für die Parkinson-Demenz, jeder zweite Parkinsonpatient erleidet das Schicksal einer Demenz.

Und die dritte wesentliche Frage in der aktuellen Parkinson-Forschung ist: Gibt es Hinweise auch auf Mitbeteiligung des serotonergen Systems, da ca. $\frac{1}{4}$ aller Patienten psychiatrische Probleme vor Ausbruch der motorischen Behinderung, hier handelt es sich insbesondere um depressive Störungen, aufweisen.

Neben der weiteren Optimierung der therapeutischen Strategien, insbesondere bei der Behandlung des fortgeschrittenen Parkinson-Syndroms ergeben sich hier wichtige Forschungsschwerpunkte von enormer diagnostischer und therapeutischer Relevanz.



HEALTH LEVEL OF THE OPERATORS WORKING IN SHIFTS

**I.A. Amanzhol MD, S.T. Onayev MD, E.A. Balayeva PhD,
A.G. Shadetova PhD, D.S. Kurmangaliyeva PhD**

*National Centre of Labour Hygiene and Occupational Diseases,
Karaganda, Kazakhstan*

Abstract

We studied working conditions of the workers employed in oil-refining factory. Dynamic monitoring of the functional state of operators throughout the shift showed that an adequate rest after shift can maintain high levels of major systems functioning, and mental and physical performance, as well as reserve capacity of the body throughout the day and night shifts. In the transition from daytime to night shifts, the rest between shifts is 8 hours, which is not enough and has an unfavorable effect on the workers' performance.

Keywords

oil refining, production factors, shift, mental and physical capacity, health.

INTRODUCTION

Development of oil production and refining industry of Kazakhstan due to its economic and social attractiveness led to the development of new and alternative forms of organizing production which is rotational method of work which also includes extended (12 hours) day and night shifts. The influence of this form of production (12 hours shifts and 2 weeks shifts) on the health of employees is not studied well enough and is a serious problem of labor hygiene.

Studying the effects of different stressors for 12-hour shift regime work on the functional state of the organism is of interest because the rotational and night work causes changes in the normal course of the biological clock of an organism that effects on maintaining the operating state for a sufficient level of efficiency (Bobko N. A., 2006, Victorov V., Kamensky, Yu.N., Kirpichnikov A.B., 1996).

Shift and especially expedition rotational methods of work produce adverse in the health of workers. These changes are caused by tension and spending of organisms' functional reserves in the process of adaptation to unusual rhythms of work and rest from the strain of social and biological rhythms. (Shustov V. Ya., Korolev V.V., Trubetskov A.D., 1995; Yushkova O.I., Kuzmina L.P., Poroshenko A.S. et al, 2008).

In this connection, nowadays it has become necessary to conduct additional studies of health of the workers employed in manufacturing where labor organized by expeditionary-shift method is a prerequi-



Amanzhol Iztileu Amanzholuly
MD, Associate Professor, Director
akjo@inbox.ru

site for appointment of workmen's compensation and the rationale for the regime of "work and rest".

OBJECTIVE IS to investigate functional state of operators in the dynamics of shift in expedition-rotational method of labor.

MATERIALS AND METHODS

The objects of the research which was a complex of hygienic and physiological studies were jobs and working operators serving the installation of "Tengizchevroil" gas processing plant. Psychophysiological studies covered 30 operators at the average age of 38.3 ± 1.0 and working experience of 9.8 ± 0.5 years. All patients were divided into two groups. Group 1 (82.5%) included operators occupied with processing equipment at the facilities of the plant. Group 2 (17.7%) included operators watching the progress of the technological process from the remote control. Physiological examinations were carried out to all operators 4-fold in the dynamics of shifts: in the beginning and end of day and night shifts for 14 days shift. Analysis of outcomes was performed taking into account the specifics of the operations and organization of the labor process.

Estimation of the functional state of the respiratory system was conducted by spirometry on a portable spiograph (SMP-21/01- "P-D", Russia) which gives the following indicators: vital capacity (VC), expiratory reserve volume RVexp; inspired reserve volume RVinsp; respiration rate (RR); tidal volume (TD); minute volume of respiration (MVR); maximum ventilation of lungs (MVL). Parameters for ventilation index (VI) and breathing reserve (RD) were obtained by calculation.

Status of central hemodynamics was studied using traditional clinical methods. All operators were

measured heart rate reduction states (HR), systolic (SBP) and diastolic (DBP) blood pressure (Korotkov). According to the results of physiological studies adaptive capacity by Berseneva (AC) and functional state index by Pirogov (FSI) were additionally calculated.

Functional state of the operators' central nervous system was studied by the method of reflexometer using a computer program. Hidden time of sensory-motor reactions: simple auditory and visual-motor reactions, complex auditory and visual-motor reactions were recorded.

Psychological status of the operators was studied by Eizenck tests (expressed in whole introversion and emotional stability), Spielberger-Hanin (re-active and trait anxiety). Mental stress was determined by questionnaire of T.A. Nemchinov, violations of the vegetative status were determined by the Wayne questionnaire, state of health by the form of health self-assessment of Afanasiyev.

Over a 12-hour shift (beginning and end of shifts) and the dynamics of 14 day shifts (at 7.00 a.m., 5.00 p.m., 7.00 p.m., 5.00 a.m.) mental efficiency of operators was registered by the blank method of Anfimov. When conducting three tests the number of symbols, the number of correctly detected symbols and the number of different errors were traced. To identify somatic illness, activity of the nervous system and emotional state a letter-hopping method "SUN" was used.

Subjective opinions of operators on the impact of various factors and conditions on their health, the prevalence of complaints, the methods of organizing work and life were analyzed in the interview questionnaire which included 50 questions. Each of these characteristics has been evaluated by both average indicators and individually for each operator. Statistical data analysis was conducted using the statistical package «Statistica», version 5.5. to determine average and dynamic changes of indicators for the operators of designated groups and Fisher and Student's test for 95% reliability.

RESULTS

While assessing labor conditions at the sites of gas processing plant it was established that in the normal course of the technological process operators of group 1 served technological equipment at various installations of the plant during the equipment inspection and fill in regime lists.

Conducted physiological studies of operators of group 1 showed that by the end of the shift there was increase in cardio-respiratory system of operators of Group 1 which demonstrated the pressure growth, which was accompanied by increase in peripheral vascular tone by 43.2% ($p < 0.05$) with increasing

sympathicotomy ($p < 0.05$) forming workers' tension. Rising of additional volume (AV) to a 0.701 to 0.77 l ($p < 0.001$), breath frequency from 16.4 to 18.1 1/min ($p < 0.001$), minute volume of respiration (MVR) from 11.4 liters to 13.9 liters ($p < 0.001$) not exceeding normal range, allowed the body to cope with the imposed loads. However, the reduction of breathing reserve (BR) from 0.92 to 0.899 conditional units ($P < 0.001$), as well as the increase in VI from 3.02 to 4.03 arbitrary units ($P < 0.001$), indicative of wasteful consumption of reserves of breath, which could cause a drop in performance and was regarded by us as fatigue.

A slight increase in DBP from 74.4 to 75.4 mm Hg (to 1.3%) and TPVR from 1398 to 1429 dyn/cm² * from 10^{-5} (to 2.2%) with a significant increase in activity of the respiratory system of MOD (to 17%) determined the decrease in physical performance in employees of group 2 by the end of the shift. Concentrated mental activity with a high psychological stress in the conditions of hypodynamic led to mismatch of synchronous activity of the respiratory and cardiac component and manifested inadequate stimulation of respiration with increasing frequency (8.5%) and depression (to 7.6%). The formation of these processes during the change reduced the reserves of the respiratory system and was associated with low physical activity.

Organization of labor process in the dynamics of the day was reflected in the integral indicators. Gradual transition of the functional state of the organism from the level of "below average" (Index of Functional Status (IFS) = 0.51 arbitrary units (a.u.)) in the morning to the level of "medium" (IFS = 0.57 a.u.) in the evening reflecting the influence of physical tension related to the movement within the working area. In the operators of group 2 IFS remained unchanged throughout the entire shift, corresponding to the "medium" level.

The indicators characterizing the state of the neuromuscular system which are the power of right and left hands remained unchanged in the operators of group 1 throughout the work. In the workers of group 2 the force of both hands during a change did not much diminish: for the right hand it was from 40.2 kg to 37.2 kg, and for the left hand it was from 40.3 kg to 37.2 kg (4.7% and 7.9%). Minor and frequent movements of regional minor groups of muscles when work on a PC, fixed position of the body during the shift without significant physical tension caused the identified changes and were the reflection of the developing working-fatigue in the system

Changing the status of the central nervous system during the change in the operators reflect the particular nature of work and the resulting slight fatigue towards the end of the shift. In individuals of group 1

to the end of the shift we determined the displacement of the balance of nervous processes in the cortical link of the auditory analyzer towards slowdown, which was probably due to the periodic location of the working groups in areas with significant noise emission. Features of work of group 2 operators' who monitoring the progress of the displayed production process, requires exercising constant vigilance and readiness to respond quickly to any changes shown on the display. This is shown in the dynamics of the central nervous system functioning. Audible and visual indexing indicating the course of the technological process in the conditions of sufficient light and no noise interference lead to activation of nerve processes in the cortical areas of the visual and auditory analyzers that determine the quality of performance set by labor problems. By the end of the shift hidden time of both simple and complex sensor-motor reactions of different modalities decreased (Figure 1). Shortness of complex sound-motor reactions decreased to 30% and visual-motor reactions decreased to 13% by the end of the shift that indicated the displacement of the nervous processes balance in the direction of excitation in the analyzer regions of the cortex.

At the beginning of group 1 operators' change there was a very low value of health and mood (2.7 and 2.9 points), while the indicators of activity were within the optimal values (5.0 ± 0.1 points). The mismatch of these three indicators showed some pre-launch tension of the organism at the beginning of a shift. The increase of the values of well-being and mood ($p < 0.01 - 0.001$) (to 19.4% and 9.4%) during the shift reflected adaptation of the workers' organisms to the conditions and nature of work. Declining of activity to 4.5 points ($p < 0.001$) by the end of the working shift indicated the development of the beginning of fatigue.

Higher baseline values of health and mood making 3.1 and 3.4 points at low values of activity (4.49 ± 0.15 points) were identified at the beginning of the change in group 2. The mismatch of these parameters at the beginning of the change also reflected the pre-launch tension of the body, but not so clearly expressed as in the operators of group 1. Further improvement of health, mood and decrease in activity towards the end of the change is observed as a sign of adaptation of the organism to the nature of work.

Dynamics of mental work capacity of the operators of the allocated groups during the extended work shift reflects the features of the organization of work and nature of the entry requirements to higher nervous activity of the operators. So, in the operators of group 1 with a decrease of the quantitative characteristics of the tests towards the end of shift the quality of their performance did not change, and on the contrary, the number of errors decreased, especially when perform-

ing simple tests (25–27%). Features of stereotypical working operations under hypodynamic conditions and in the mode of sensory expectations of the workers of group 2 identified the dynamics of changes in mental capacity, which was shown in both reducing the quantitative characteristics of the tests (7–18%), and in increasing the number of erroneous actions (in 17–37%). The biggest change was achieved when a complex test with differentiation and switch of attention was conducted. These functions were central in occupational safety in group 2 operators.

Among patients of group 1 there were 68% of introverts, 32% of extraverts, while among the operators of group 2 there were no extraverts at all (Figure 2).

There were emotionally unstable persons in both groups of operators, but if in Group 2 their number did not exceed 10%, in group 1 they were almost half of the surveyed persons (40%).

Thus, group 2 of the operators was dominated by the number of phlegmatic persons who did not experience psychological discomfort in both standby regime for a signal, and who had sufficient qualities for adoption and implementation of fast decisions and actions.

When comparing the functioning of the central nervous system in the morning time during the watch the balance of nervous processes in hearing and visual cortex in the organization of work during a day shift was standard, but there was also a shift of balance towards excitation before working in the night shift. This is a proof of the rest sufficiency to recover the balance of nervous processes. Sharp strengthening of inhibitory processes (40–60%) in the transition to the night shift reflected not only adapting to the conditions of work, but also violations of the chronobiological rhythms. Gradual accumulation of fatigue in the dynamics of the day shift in the cortical link of the hearing analyzer (in 4–26.3%) during the night shift increased (up to 25.4–34.6%). Joining the aforementioned processes of fatigue in the visual cortex (in 34.4–42.5%) determined retention of inhibition in the dynamics of the night shift. Transition of work to the night shift was the most tedious and stressful for the operators' CNS which was kept in the operators till the end of the watch for the next 7 days.

A similar pattern was found with regard to mental capacity, which was improving during 7 days in one shift in a "before work" state qualitatively (to 13.2–18.4%) and quantitatively (to 27.9–38.5%).

A level before work at night change for 7 consecutive days of the shift was declining gradually not only in the volume of watched signs (to 5–16%) and deleted signs (to 7–11.8%), but also by reducing the error (in 22.4–67.5%). This process demonstrated strategy for maintaining quality by reducing the quan-

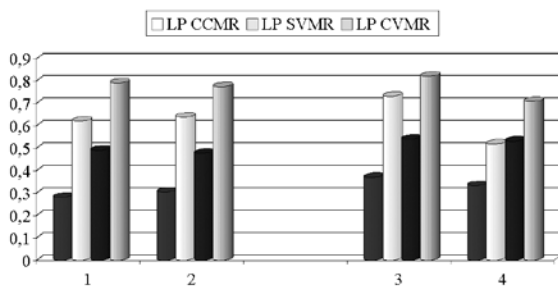


Figure 1. Indicators of the central nervous system in operators of professional groups 1 and 2 in the dynamics of the working shift

Note: LP SHMR – latent period of simple hearing motor reaction, LP CHMR – latent period of complex hearing motor reaction, LP SVMR – latent period of simple visual-motor reaction, LP CVMR – latent period of complex visual-motor reaction; Abscissa axis: 1, 2 – Group 1, 3, 4 – Group 2; 1, 3 – beginning of the shift, 2, 4 – end of the shift

titative characteristics of the. In the transition from day shift to work at night shift the background values of mental capacity decreased due to quantitative (to 13.4%) and qualitative characteristics, especially when performing tests with switching attention (213%). Comparing the mental abilities at the end of the day during the first week of the shift it should be noted that the quantitative and qualitative characteristics of simple tests reduced gradually (to 10.3–13.7% and 47.8%), but quality and quantity of complicated tests with differentiation of attention remained unchanged. The transition from day shift to work at night revealed only a slight decrease of mood. Dynamics of “before work” levels of health and mood of the night shift operators gradually increased to the end of the shift ($p < 0.01$), whereas their activity decreased ($p < 0.01$). Decrease of such indicators as health and mood corresponded to fluctuations of daily biorhythms. In spite of insignificant decrease in activity towards the end of the shift, its value remained at a sufficiently high level, indicating the restoration of the reduced capacity of the organism to the beginning of the next shift. This allows the operators to maintain a sufficiently high level efficiency during the entire 14 days shift.

Neuro-psyche tension (NPT) recorded in the beginning of the shift (38.7 ± 1.5 points) was regarded by the operators as “weak detensive”. In the dynamics of the first week its severity did not change, remaining at the level of 34.5 ± 1.5 points, and remained “weak detensive” till the end of the shift. Transition of work to the night shift made an effect on the operators’ organisms manifested by formation of neuro-psychological stress of “intensive” level (up to 61.0 ± 1.6 points, $p < 0.01$).

Dynamics of changes of reactive anxiety (RA) over the shift reflected slight reduction of PT to the end of the first week (up to 32.4 points) and keeping it at the average level (35–36 points) before the end of work.

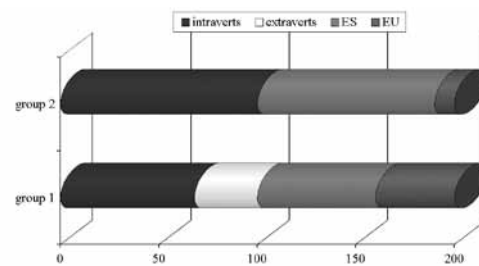


Figure 2. Prevalence of persons with different typological profile among operators of groups 1 and 2

Note: ES-emotionally stable, EU-emotionally unstable.

This allows us to say about quick involvement of operators into the work and preserving their confidence in their own capacity to implement it. However, an analysis of vegetative feeling obtained by the Wayne test testified to the emergence of a number of autonomic dysfunctions (17.0 ± 1.6 points) to the end of 14 days shift. Working in the day shift was characterized in the operators by preservation of heart blowout and peripheral vascular resistance, weakening of sympathetic influences till the end of the shift, accompanied by increasing vascular resistance and decreased heart rate. Reconfiguring functioning of the cardiovascular system during shifts’ change was accompanied by increase in all circulatory dynamics parameters except for stroke volume of blood that was regarded as a system tension, manifested as a less favorable response of the system on the workload due to amplification of heartbeat and reduction of peripheral vascular resistance. Tension of circulatory dynamics formed in the second part of the shift was maintained until the end and determined reduction in work from the “average” to a lower level “below average” (Figure 3).

56% of group 1 operators and 80% of group 2 operators assessed their health status as “good”. 40% of employees of group 1 estimated their health status as “satisfactory”, and 4 % of the respondents could not answer this question. In the second group 10% of the interviewed operators considered state of their health as “satisfactory”.

Half of the respondents, both in the first (56%), and in the second (50%) groups believed that adverse working conditions affect their health and life duration, 30–60% named environmental factors, and 33–40% of the employees chose the answer “life conditions”.

Analysis of the diseases nature identified by the poll showed that chronic diseases in group 1 made up the bulk (20%), and chronic and acute diseases made 12% (Table 1). People of group 2 indicated acute (30%) or chronic diseases (20%), and also occupation injuries (10%).

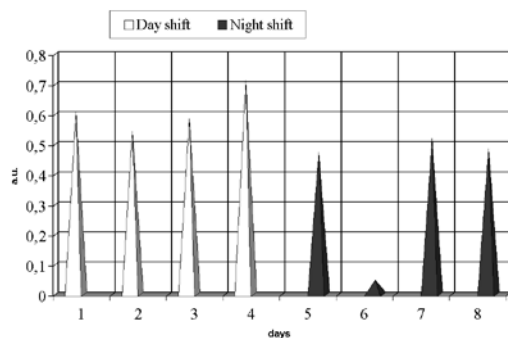


Figure 3. Change in CPI in operators in the dynamics of the shift

Note: horizontal axis: 1, 2 – beginning of the day shift, 3, 4 – end of the day shift, 5, 6 – beginning of the night shift, 7, 8 – end of the night shift;

Table 1. Nature of diseases among workers according to the poll

Questions	Answers	Distribution, %	
		Group 1	Group 2
Nature of diseases	Acute diseases	8	30
	Chronic diseases	20	20
	Chronic and acute diseases	12	-
	Occupational diseases	8	-
	Occupational injuries	-	10
	Household injury	8	-
	Nursing process after smb	4	-

As the operators of group 1 were undergone to industrial noise during the work process, 56% of the respondents identified it as a factor disturbing the implementation of work.

In addition, employees of the same group noted such factors of production, as dust and fumes in the workplace (44% each), vibration and low temperature (28%), presence of drafts (16%) and low luminosity (12%) as interfering.

The operators of the central control panels often complained about non-optimal microclimatic conditions: drafts (50%), low temperature (30%), high humidity (20%) and weak illumination (20%). The overall level of gas contamination at the industrial site produced negative reactions in 40% of the operators.

The nature of work performed by the operators of group 1 requires strain of attention (92%), and sensor systems (60%), and in group 2 strain of attention was required by 10 % and sensor systems – 60% of the respondents.

More than a half (60%) of group 1 and almost all (90%) operators of group 2 noted that the main production processes are performed by them in a rapid and very rapid rate. High length of work places in 50% of group 1 determined significant movement in the working area in both horizontal and vertical planes.

Peculiarities of organization of the production process and duration of the working shifts (12 hours)

were the cause of the high prevalence of complaints for reduction of efficiency during the work in 60% of workers in the first and 64% in the second professional groups. In this case the bulk of the operators (up to 60% in group 1 and 50% in group 2) noted moderate fatigue both at work at night and at work in the day shift. 4% of group 1 and 10% in the second group were very much tired. 16% of group 1 and 40% of group 2 did not experience fatigue during the day shift, and at night their number was higher: 24% of group 1 and 40% in the second group.

Reduced performance capacity during the change in workers of groups 1 and 2 was accompanied by the formation of a number of autonomic disorders. Among the most common were headache (16% and 20%), heaviness in the legs (30% and 60%), drowsiness and sudorrhea (10% and 12%), irritability (in 4% and 10%). Working in the night shift caused more expressed manifestations of fatigue in the form of drowsiness (30% and 36%) among both groups.

CONCLUSIONS

1. Impact of adverse factors of production in patients of group 1 caused increase of peripheral vascular tone on the background of sympathicotony and increase of respiratory, resulting in formation of inhibitory processes in the cortical link of the auditory analyzer.
2. Under the influence of unfavorable factors of production in patients of group 2 we found shift of the balance of nervous processes towards excitation, reduction of quantitative characteristics of efficiency, activation of neural processes, without going beyond the limits of physiological norm and reflecting development of work tension.
3. In the transition from daytime to night shifts the rest between changes lasting for 8 hours is insufficient and may cause the development of fatigue, and reduction of functional reserves.

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REHABILITATION OF PATIENTS WITH COMBINED PROFESSIONAL PATHOLOGY

I.A. Amanzhol, M.B. Otarbayeva, A.U. Amanbekova, O.V. Grebeneva, N.M. Zhanbassinova

National Centre for Occupational Hygiene and Occupational Diseases, Karaganda, Kazakhstan



Maral B. Otarbayeva, MD
Associate Professor; Head
of the Department of
Management of Scientific
Research

TOPICALITY

Effective way of reducing the professional vertebro neurologic diseases – is improvement of working conditions and the expansion of primary prevention [1].

In this connection, there is a need to develop therapeutic and rehabilitative measures, namely in combined forms of occupational pathology and the creation of new and more effective treatment options for diseases of the peripheral nervous system, since the vertebral pathology and vibration disease are diseases of the peripheral nervous system, as well as massive comprehensive

survey showed that the professional pathology serves as a “mask” of heavy somatic diseases, resulting in patients not timely diagnosis and adequate treatment is not carried out that generally affects the “quality of life” of patients [2, 3]. According to [4], physical exercise influence the trophic function of the nervous system, there is a reflex change in the trophic, adequate to functional irritation. Effect of exercise manifests itself in the challenging and normalized their influence on the regeneration processes of damaged tissues.

In combination with acupuncture is very effective use of autogenic training, breathing exercises, special physical exercises.

THE AIM of the study was: evaluation of the effectiveness of the complex of rehabilitation measures for patients with combined professional pathology (vibration disease and vertebral pathology) – combined pathology.

MATERIALS AND METHODS OF RESEARCHING

Rehabilitation activities were carried out on two groups of patients associations Coal Department Stock Company Mittal Steel Temirtau with combined

professional pathology with moderate-marked pain syndrome, which passed examination and treatment at the National Centre for Occupational Hygiene and Occupational Diseases MH RK. The average age of patients was $47,7 \pm 12,4$, seniority $21,4 \pm 2,43$ year.

Group 1 (20 person) – acupuncture with treatment-sports complex (therapeutic exercise); Group 2 (20 person) – physiotherapy + exercise therapy. In addition, treatment included traditional comprehensive treatment, including medicines (nonsteroidal anti-inflammatory drugs (NSAIDs)), cardiovascular drugs and drugs improve nerve conduction) (traditional therapy), which was performed in both groups.

Our patients underwent acupuncture on the three zones (two pairs of symmetric points in common), segmental area (2 pairs of symmetric points in common), on-site pain (one pair general, 2 pairs of segmental and 1–2 pair of symmetric local points). Therapeutic exercises done comprehensively to our patients (an exercise program has been distributed in the form of reminders for each patient to better fixation).

Evaluating the effectiveness conducted by the following indices of rheovasography: time of rapid blood flow, regional blood volume, minute pulse, the elastic modulus, an index of rapid filling, rheographic indicator of venous outflow.

And also take into account the parameters characterizing the components of neuromuscular transmission: the M-response amplitude of the motor fibers for the peroneal and the tibial nerve, the rate of impulse conduction in motor and sensory fibers of the peroneal and tibial nerves, residual latency.

Statistical data processing was carried out according to standard methods, using specialized software for statistical analysis – tabular processor «Microsoft Excel» and the program «STATISTICA 6.0» (company StatSoft, USA). For comparison of intergroup data, the method of nonparametric statistics U Mann-Whitney test for independent variables was used.

RESULTS OF THE RESEARCH

The results showed the rationale for therapeutic and preventive measures acupuncture + therapeutic

exercise + drug therapy, which leads to a reduction of pain, relieve muscle tension in the back, blocking the pain impulses traveling from the periphery, at various levels of the central nervous system, promote activation of functional reserves of an organism. Muscular work, enhancing the dominant motor analyzer, changes the function of internal organs, particularly the circulatory system and respiratory system. Work of skeletal muscles in the light of the concept of motor-visceral reflexes should be considered as a stimulator and regulator of responses, particularly the circulatory system. Dosage muscle activity in the application of physical exercise should be regarded as a factor contributing to the restoration of vegetative functions, violated by the disease. It is known the regulatory influence of moderate exercise on the function of the cardiovascular system. This influence is expressed in increasing energotropic and trophotropic effects on the heart muscle, mobilization of the vascular system and extracardiac factors of blood circulation and blood flow device as a whole to the needs of exchange [5–7].

In the course of treatment and prevention activities have revealed the following. In individuals with a moderately pronounced syndrome after correction (acupuncture + therapeutic exercise + drug therapy) significantly increased the indicators reflecting the tone of large arteries: a time of rapid filling of the alpha 1 (CI 0,05–0,1, $P < 0,05$), more from pain; decreased rate of alpha / RR (modulus), (CI-15,6–23,4, $P < 0,02$), slightly higher from the pain. Increased the index of rapid filling, especially from pain (CI 51,1–58,4; $P < 0,001$), improved venous outflow PBeta more of the vessels and the femoral pain syndrome (CI 1,04–2,6). Improved the indicators characterizing the intensity of arterial blood flow in the form of increased minute pulse of regional blood volume, with both sides in the vessels of hip and thigh (CI 2,04–2,6, $P < 0,001$, $P < 0,02$), significantly increased the parameters reflecting volume pulse blood filling – rheographic index (CI 0,3–0,4, $p < 0,001$). As can be seen from reovasographical data, improved all main indicators – pulse blood filling, vascular tone, elasticity of the vascular wall and the venous outflow.

Found that, in the course of treatment significantly improved indicators of the components of neuromuscular transmission: the M-response amplitude of the motor fibers – the effectiveness of treatment 56,6–42,8% (CI 8,7–10,1; $P < 0,001$) in peroneal and tibial nerve respectively; increased speed of the pulse motor 28,6–19,3% (CI 3,5–4,4, $p < 0,02$) and significantly by touch (42,3–54,9%) fibers of the peroneal and tibial nerves (CI 34,3–47,01, $P < 0,001$), slightly smaller, but also improved performance on the residual latency 61.1–23.5% (CI 31,1–41,6; $P < 0,001$). High

efficiency of acupuncture, subject to standard rules is achieved only when individual choice points of impact, which we used for the correction. Acupuncture was aimed at correcting the tissue perfusion, muscle relaxation, as well as blocking the pathological extero, proprioceptive and interoceptive impulses.

In individuals with a combined pathology with a moderately pronounced syndrome treated with physiotherapy + drug therapy showed significant improvement in indicators of the intensity of the arterial blood flow in the form of increased minute pulse of regional blood volume, with both sides in the vessels of hip and thigh (CI 2,04–2,6, $P < 0,02$), increasing the index fast filling more of the pain (CI 46,7–53,6; $P < 0,001$) increase in the volume pulse blood filling – (rheographic indicators) (CI 0,3–0,4 $P < 0,001$). Improving the condition of patients with combined pathology data confirm electroneuromyographic research, improvement of which was less pronounced in the group treated with physiotherapy + therapeutic physical exercises + drug therapy.

Patients treated with physiotherapy + therapeutic physical exercises + drug therapy data electroneuromyographic research also showed improvements, which were less pronounced, but significant. Found that in patients with combined pathology training with moderate syndrome of increased number of functioning motor units in the muscle (according to the amplitude of the M-response, CI 8,7–10,1; 43,3–44,6; $P < 0,001$), improved the flow of demyelinating processes, as evidenced by the performance of speed of the pulse of motor and sensory fibers (CI 34,3–47,0, $P < 0,001$), improved the state of the terminal unmyelinated fibers on indicators of residual latency fibular and tibial nerve (CI 3,5–4,4, 4,7–5,6, $p < 0,001$).

As seen above, the most positive changes after the correction are noted in patients taking the physiotherapy + therapeutic physical exercises + drug therapy. This can be explained by the fact that in the integumentary tissues, and especially in the skin, muscles, tendons and ligaments are local zones of innervation of the maximum used in the practice points (biologically active point). The latter have a definite innervation liaison with relevant bodies, systems, and sites that provide focus on the impact of these structures during stimulation of these points.

Thus, the results of our treatment of persons with combined pathology we achieved a guaranteed functional outcome. Those receiving the correction of the physiotherapy + therapeutic physical exercises + drug therapy, more susceptible to the positive dynamics, not only at the end of the course the basic treatment of spine, but in the late periods after treatment of spine and are more durable and long lasting

in nature, which greatly improves the quality of life of these patients.

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EVALUATION OF MORBIDITY OF THE POPULATION, RESULTS OF MEDICAL AND BIOLOGICAL RESEARCH IN UST-KAMENOGORSK CITY

A.U. Amanbekova, L.K. Ibraeva, G.N. Azhimetova, G.T. Igimbaeva, B.A. Abdigozhina

*National Centre for Occupational Health and Occupational Diseases,
Karaganda, Kazakhstan*

The problem of adverse influence of factors of environment on a state of health gets every year the increasing urgency [1,2]. Health reflects an ecosystem condition as a whole, is the generalized indicator of quality of inhabitation and its influence on ability to live of people [3–6]. Last decades the increase in prevalence of illnesses of separate nosological forms which is caused by environmental contamination is observed. As a subject of discussions among professionals the contribution of environmental contamination and its separate kinds to growth of disease and death rate of the population, in view of complexity of interaction of numerous factors of influence and difficulties of revealing of factors of diseases [7–9] serves.

Adaptable mechanisms of the person don't keep up with fast changes of environment. Negative factors of an urbanization have sharply increased in cities – noise, vibration, small mobility of the population, the accelerated rhythm of life, huge number of irritants. It involves infringement of natural biorhythms of a human body, increase in mental and emotional loading, stressful conditions [10].

The majority of diseases which are investigated in socially-hygienic monitoring are the ecologically dependent illnesses which communication with environment factors exists, but it isn't so strong to be obvious. Thereof, the proof of presence of communication between a state of health of the population and a state of environment is an uneasy problem.

Thus, environmental contamination by harmful substances and their influence on health of the person is one of the major problems for the today, demanding the immediate decision.

PURPOSE OF THE STUDY

To assess the morbidity of the population of Ust-Kamenogorsk city on the results of biomedical research.

MATERIALS AND METHODS

The object of the study was the adult population of two districts of the city of Ust-Kamenogorsk

(region «CSM» and region «Zashita»), aged 18–59 years, living in the territory of at least 10 years old and not working in harmful working conditions, total surveyed 772 people. The control area is selected Shuchinsk city, located in the resort area, where 635 people were surveyed.

Surveyed individuals were questioning according to card medical examination, approved by the local Ethics Commission (№ 13 of 24.04.2010), have been examined by the therapist before inspection, it had been conducted laboratory researches (the general analysis of blood, the biochemical analysis of blood, immunological indicators, thyroid gland hormones), an electrocardiogram, function of external breath. Under indications, for final statement of the diagnosis, additional kliniko-functional researches (ultrasonic of a gastroduodenal zone and kidneys, a thyroid gland) were conducted.

Data were collected on the nature of the cohort, cross-sectional, double-blind studies. For qualitative variables and quantitative variables with abnormal distribution of the expected median and 25% and 75% quartiles. Assessment of relative risks was carried out on the value of χ^2 . Risk assessment determined the odds ratio (OR) confidence interval (CI), the relative risk (OR), etiological fraction effects (EF), the absolute risk (AR), the percentage of associated risk (AKP) and the associated risk population (SPR).

RESULTS

In the area of «KSHT» Ust-Kamenogorsk city has been viewed 342 people. Among the surveyed residents of the area «KSHT» Ust-Kamenogorsk city, 35.9% of the cases were healthy, the other 64.1% of cases regarded as the sick, among them a group of people with newly diagnosed disease were 70.3% of cases, and persons with chronic disease – 29.7% of cases. On the basis of the district health center «Zashita», Ust-Kamenogorsk city was examined 430 people of which 45.6% cases were healthy, the rest 54.4% are regarded

as patients (54.7% – persons with newly diagnosed disease, 45.3 % – persons with chronic disease).

Among residents Shuchinsk city 32% of cases surveyed were healthy, the other 68% are regarded as patients, of whom 84% were individuals with newly diagnosed disease.

In the surveyed population area “KSHT” of Ust-Kamenogorsk city, the most frequent disease was first identified by the cardiovascular system – 47.4% (of which, 95.7% of the cases was hypertension), gastrointestinal tract – 39.6% (of which 24% of chronic choletsistopankreatit and 23% of chronic gastritis), urogenital system – 27.9% (of which, 95.4% of chronic pyelonephritis), the endocrine system – 28.6% (of which, 97.1% of hyperthyroidism) (Table 1).

endocrine (10.9% of cases, of which 78.6% represented hyperthyroidism). Diseases of the cardiovascular system in 72% of cases presented arterial hypertension, diseases of the gastrointestinal tract were recorded more often chronic choletsistopankreatit (33.3%) and chronic gastritis (30.9% of cases) (Table 2).

In the surveyed population Shuchinsk city most frequent first identified diseases of the urogenital system - 55.4% (including 52% – against a background of chronic pyelonephritis kidney stone disease, 33% – chronic pyelonephritis against a background of nephroptosis), the endocrine system – 43.2% (60% of them - hyperthyroidism), gastro-intestinal tract – 36.8% (including 42% – chronic cholecystitis, 23% – chronic gastritis) and cardiovascular system

Table 1. Structure of the newly identified disease therapeutic profile for the systems surveyed in the residents' KSHT “Ust-Kamenogorsk city

The classes of disease	Total number		Male		Female	
	Abs	%	Abs	%	Abs	%
Hematopoietic system	5	3,2±1,4 (2,9:3,4)	1	2,0±2,0 (1,5:2,6)	4	3,8±1,8 (3,4:4,2)
Endocrine System	44	28,6±3,6 (21,3:35,9)	2	4,1±2,8 (3,3:4,9)	42	40,0±4,8 (30,4:49,6)
Cardiovascular system	73	47,4±4,0 (39,3:55,4)	28	57,1±7,1 (42,9:71,2)	45	42,9±4,8 (33,2:52,6)
Respiratory System	23	14,9±2,8 (14,4:15,4)	8	16,3±5,3 (14,8:17,8)	15	14,3±3,4 (13,6:14,9)
Gastrointestinal tract	61	39,6±3,9 (31,7:47,5)	19	38,8±6,9 (24,9:52,7)	42	40,0±4,8 (30,4:49,6)
Urogenital System	43	27,9±3,6 (20,7:35,1)	11	22,4±5,9 (20,7:24,1)	32	30,5±4,5 (21,5:39,5)
Musculo-skeletal system	5	3,2±1,4 (2,9:3,4)	1	2,0±2,0 (2,6:1,5)	4	3,8±1,9 (3,4:4,2)

Note: in parentheses are 95% confidence intervals

Table 2. Structure of the newly identified disease therapeutic profile for the systems surveyed in the residents 'protection', Ust-Kamenogorsk city

The classes of disease	Total number		Male		Female	
	Abs	%	Abs	%	Abs	%
Hematopoietic system	4	3,1±1,48 (2,83:3,38)	-	0	4	5,9±2,01 (5,23:6,61)
Endocrine System	14	10,9±2,66 (10,4:11,39)	3	5,0±1,86 (4,29:5,75)	1	16,2±3,15 (15,13:17,3)
Cardiovascular system	53	41,4±4,2 (32,9:49,8)	4	40,0±4,18 (31,63:48,37)	9	42,6±4,22 (34,15:51,05)
Respiratory System	16	12,5±2,82 (12,0:13,02)	16	26,7±3,78 (19,14:34,26)	10	14,7±3,02 (13,67:15,76)
Gastrointestinal tract	46	35,9±4,09 (27,7:44,1)	21	35,0±4,07 (26,85:43,15)	25	36,8±4,12 (28,56:45,04)
Urogenital system	29	22,7±3,58 (22,0:23,36)	15	25,0±3,69 (17,6:32,,)	24	35,3±4,08 (27,13:43,47)
Musculo-skeletal system	5	3,9±1,65 (3,6:4,2)	3	5,0±1,86 (4,29:5,75)	2	2,9±1,43 (2,42:3,41)

Note: in parentheses are 95% confidence intervals

The structure of newly identified disease therapeutic profile of the surveyed systems, residents of the area “Zashita”, the Ust-Kamenogorsk city were the most common diseases of the cardiovascular system (41.4%) and gastrointestinal (35.9% of cases). Several less frequent diseases of the urogenital (22.7% of cases, of which 94.5% were chronic pyelonephritis) and

– 31.6% (including 74% – high blood pressure) (Table 3).

In assessing the risk of morbidity, Ust-Kamenogorsk city, compared with the population Shuchinsk city a statistically significant difference by the value of χ^2 (31,5) with a high relative risk (2,07) and an odds ratio (2,36) (Table 4).

Table 3. Structure of the newly identified disease therapeutic profile of the surveyed residents by systems Shuchinsk city

The classes of disease	Total number		Male		Female	
	Abs	%	Abs	%	Abs	%
Hematopoietic system	51	14,13±1,83 (13,9:14,3)	4	5,4±2,63 (4,81:6,03)	47	16,4±2,19 (16,1:16,7)
Endocrine System	156	43,2±2,61 (37,9:48,4)	36	48,6±5,81 (36,9:60,2)	120	41,8±2,9 (35,9:47,6)
Cardiovascular system	115	31,85±2,45 (26,9:36,7)	19	25,7±5,1 (15,54:35,8)	96	33,4±2,78 (27,8:38,9)
Respiratory System	64	17,7±2,01 (17,5:17,9)	12	16,2±4,28 (15,2:17,2)	52	18,1±2,27 (17,8:18,4)
Gastrointestinal tract	133	36,8±2,54 (31,7:41,9)	25	33,8±5,5 (22,8:44,8)	108	37,6±2,86 (31,9:43,3)
Urogenital system	200	55,4±2,62 (50,17:60,6)	34	45,9±5,79 (34,4:57,5)	166	57,8±2,92 (51,9:63,6)
Musculo-skeletal system	30	8,31±1,45 (8,16:8,46)	5	6,7±2,9 (6,04:7,39)	25	8,7±1,66 (8,5:8,89)

Note: in parentheses are 95% confidence intervals

In this high risk due to cardiovascular diseases among the male population of Ust-Kamenogorsk city, g, which represented 72% of hypertension ($\chi^2 = 4,2$) (Table 5).

In such a way, during the medical examination of population of Ust-Kamenogorsk city, more than 60% of the surveyed people recognized by patients. In this case, a group of people with newly diagnosed disease were the most common diseases of the cardiovascular system, gastrointestinal tract and urogenital system. In the comparative assessment of the relative risk to residents of Ust-Kamenogorsk city, compared with Shuchinsk city found higher risk (1.45) by cardiovascular disease among men surveyed systems.

Table 4. Risk assessment by diseases of various body systems, Ust-Kamenogorsk, compared with the morbidity of the population Shuchinsk city

city	RC	CI	RR	EF	AR	PCR	CRP
Ust-Kamenogorsk*	2,36	1,75:3,21	2,07	51,6	10,5	99,5	30,4

Note: * – statistically significant difference in the $\chi^2 > 3,84$

Table 5. Risk assessment by diseases of the cardiovascular system of the male population of Ust-Kamenogorsk city, compared with the male population Shuchinsk city

system	RC	CI	RR	EF	AR	PCR	CRP
cardiovascular*	1,81	1,05:3,16	1,45	31,2	30,6	99,3	12,1

Note: * – statistically significant difference in the $\chi^2 > 3,84$

CHANGES OF THE PRODUCTION FACTORS' COMPLEX ON THE STATE OF AFFERENT SOMATOSENSORY CONDUCT WAYS IN VERTEBROGENIC SPINE PATHOLOGY IN MINERS

Zh. Battakova, Sh. Battakova, U. Amanbekov, B. Shraimanov, G. Miyanova

National Centre of Labour Hygiene and Occupational Diseases, Karaganda, Kazakhstan

Sharbanu Battakova
MD, Professor
ncgtpz@gmail.com

INTRODUCTION

Pathology of the lumbosacral spine takes about 30% of the overall morbidity, and 20–30% of all diseases of the nervous system and more than 80% of the peripheral nervous system. About 80% of all healthcare system costs accounts for the treatment of back pain [1, 2].

The prevalence of occupational diseases of the peripheral nervous system among the persons of employable age is characterized by high detectability, often with loss of employability and disability. These are the most frequent of the diseases which lead to disability of persons younger than 45 years, exceeded only by diseases of the cardiovascular system and joints. When analyzing the frequency of back pain in patients with vertebral disorders it was revealed that the pain syndrome in the lumbar region was a multifactorial problem, and production factors are risk factors of back pain [3, 4].

There is no doubt that it is important to study the spine stem mechanisms of formation of autonomic motor reflex responses to the adverse effects of the complex environment factors.

Current knowledge on the functioning mechanisms of pain and analgesia are based on anatomical and morphological, neurophysiological and biochemical studies.

Considering the problem in general, it may be noted that pathophysiological mechanisms of lumbosacral radiculopathy with pain syndrome in miners remain insufficiently studied [5, 6]. Characteristics and extent of changes on peripheral, segmental and central levels of the sensor motor system taking into account emotional-effective disorders in occupational vertebrogenic diseases are underestimated that affect the choice of making the examination of work capacity, connection of the disease with the occupation, adequacy and effectiveness of individual treatment and rehabilitation program [7, 8].

The above mentioned issues are of great practical importance, and allow to propose evidence-based

Abstract

Background

We carried out a comprehensive analysis of all parts of afferent somatosensory systems in the presence of pain of varying severity in miners. The analysis was based on modern neurophysiological studies.

Methods

We conducted the symptoms complex analysis of indicators of electrophysiological studies in patients with mild to moderate degrees of pain. The control group consisted of 28 patients.

Results

Neurophysiological changes are characterized by generalized mixed affect of the peripheral sensory nerves and 1α -afferents of H-reflex arc. The failure of systems of pain control has dominantly deafferentation character. A characteristic difference between them is also the involvement of 1β fibers (motor nerves and efferent link of the H-reflex).

Conclusions

It was found out that the data obtained allow to extend the understanding of the mechanisms of formation of neuropathic pain in the vertebral spine pathology.

Keywords

pain reception, afferent neurons, proprioception.

differential approaches to treatment and expert issues solutions for introduction into clinical practice, taking into account severity of occupational diseases of musculoskeletal system.

THE STUDY AIM

is rationale of the influence of production factors on the state of the afferent somatosensory system in the process of miners' work.

MATERIALS AND METHODS

The studies were conducted within the frameworks of the Applied Research Program of the Ministry of Healthcare of the Republic of Kazakhstan in the Republican State Governmental Enterprise "National Center of Labor Hygiene and Occupational Diseases" (NC LH OD) 0103RK, supervised by the Department of Science and human resources (2006–2009).

We conducted a neurological and electrophysiological examination of miners of LLP Zhezkazgan mining-metallurgical combine "Kazakhmys Corporation" and JSC "Arcelor Mittal" with the pain syndrome of vertebral pathology and lumbosacral spine who were patients in the neurological department of the clinic of the National Center of Labor Hygiene and Occupational Diseases. Control group were miners (28 people) who did not have signs of pain syndrome. According to outpatient medical records these patients were not registered in the dispensary at the vertebral spine pathology.

The miners were divided into 3 groups on the basis of severity of a leading clinical syndrome: group 1 included 83 miners with the pain syndrome (average age is 41.8 ± 9.6 years) – not sharply expressed degree of reflex tonic pain syndrome, group 2 included 46 miners with moderate expressed degree of reflex tonic and radicular-pain syndrome (mean age 44.6 ± 11.4 years), group 3 included 19 miners (average age is 48.0 ± 10.9 years) miners with the severe degree.

Electrophysiological study: definition of somatosensory afferent-efferent pathway, evoked potentials (EP) and brain structures for the objective assessment of functional status at different levels of specific and nonspecific afferent systems.

To record somato-sensory evoked potentials (SSEP) we used electromyograph "Neurosoft", Russia. SSEP was recorded from the surface of the head with conventional disc electrodes with the diameter of 5 mm. When recording the potentials caused by stimulation of the right median nerve, the registration was held at Yerba (over the Brachial Plexus), C7 in the cervical (above the seventh vertebra) Fz in the frontal region, C3 and C4 (zone projection of somatosensory cortex on the left and right). The respective components were identified in trass N9 (brachial plexus response), N11–N13 (cervical segments of the spinal cord), N20–R25 (zone of the cortical projection of arm) (according to the international system of electroencephalographic leads "U-20%) when recording the potentials caused by stimulation of the left and right tibial nerve.

Statistical analysis was performed on IBM-compatible personal computer Pentium using the program Microsoft Excel and statistical analysis program AnalystSoft, StatPlus, 2007 version.

The calculation of basic statistical parameters was carried out using the methods of parametric and nonparametric descriptive statistics. A comparison between different samples of data was performed using Student's *t*-test for independent samples to define levels of reliability.

RESULTS AND DISCUSSION

The main clinical manifestations of disease in the patients examined were pain in lumbosacral localization (65 patients) radiating to the lower limbs (65 patients, or 100%) of moderate and severe degrees.

The results of SSEP components in patients with occupational pathology of vertebral pain syndrome, suggest that the main neurophysiological characteristics of chronic pain syndrome in the absence of structural lesions of the brain is hyperexcitability of its afferent systems. The necessary condition for occurrence and continuation of the pain is the relative safety of specific projections carrying information to the cerebral cortex by fast conducting fibers.

In a study of indicators of SSEP it was revealed that an afferent wave of excitation, namely, pain in the ways of general sensitivity, took place in the posterior columns of the spinal cord (component N22), then through the stem sections of the brain (component N30) and later in cortex (a component of P38, R46). These curves reflect the passage of the nerve impulse to the relevant structures and can detect subclinical slowing of the pulse indicating the failure of the conduction system (Table 1).

Table 1. Indicators of amplitude characteristics of the SSEP components in patients with vertebral pathology of the lumbar spine depending on the pain syndrome

Component	Amplitude, mCB			
	Control group n=28	Control 1 n=83	Group 2 n=46	Group 3 n=19
N22	1.1±0.5	0.74±0.012	2.54±0.02*	3.45±0.03**
N30	0.8±0.3	0.59±0.06	2.48±0.04*	3.39±0.05**
P38	2.4±1.5	1.94±1.0	3.5±0.09*	4.1±0.08**
P46	2.3±1.3	2.0±0.81	3.7±0.9	4.5±0.6*

Note: * – Significant difference between the indices of the control group and the surveyed group, * – $p < 0.05$, ** – $p < 0.01$

We revealed the increase of amplitude of characteristics depending on the pain, but it is more expressed in mild to moderate degrees of pain. Thus, the amplitude of component N 22 reflecting the activation of neuronal elements of the spinal level, mainly cauda equine and medullary cone increased, with moderate-expression and expressed pain syndrome.

The amplitude of the component N30 representing the activation of the posterior columns of the spinal cord at the border of the cervical spine and medulla oblongata with mild to moderate degree increased.

Indicators of the amplitude component P38 and 46 reflecting the activation of the somatosensory cortex had tendency to increase at a moderate and significant degree of pain.

Thus, increasing the components of SSEP amplitude, interval, latency in patients with apparent pain syndrome, depression and anxiety may indicate the development of central sensitization of the conduction system (N30, P38, P46), realized in nonspecific medio-basal limbic structures of the brain [7, 8].

N10-N20 intervals characterize the conduction on the ascending pathways of the spinal cord, the interval N20-P30 is similar to the central conduction time (CCP).

In patients with the moderate degree of pain there was a significant lengthening of the intervals: N10-N13; N13- N20; N20-N30. These indicators have most significantly increased in the apparent degree of pain (Table 2).

Table 2. Parameters of basic intervals of SSEP components in patients with vertebral pathology of the lumbar spine, depending on the pain syndrome

Components	Intervals, ms			
	Control group n = 28	Group 1 n=83	Group 2 n=46	Group 3 n=19
N10-N13	7.65±1.04	12.34±2.44	15.2±2.01*	19.8±2.3**
N13-N20	8.36±1.56	15.63±2.38	18.6±3.2*	20.4±3.1**
N20-N30	16.1±1.55	28.0±3.15	32.3±2.56*	37.1±1.9**

Note: * – Significant difference between the indices of the control group and the group surveyed, * – $p < 0.05$, ** – $p < 0.01$

The increase of the interval N22-P38 with the preservation of CCP indicating a violation of the ascending pathways of the spinal cord, depending on the severity of pain in patients with vertebral lumbar pathology was marked.

Thus, under the influence of the complex factors of production (lesion of spinal roots L5-S1) there is the reaction of myelinated 1α -sensitive and motor guides. This pain syndrome occurs by stimulation of low-threshold mechanoreceptors 1β -fibers not destroyed stimuli on the background of central sensitization.

In patients with vertebral pathology with mild pain syndrome there was a significant increase in latency of N30 with a tendency to increase the component P38, P 46, and in patients with mild to moderate

degree of pain there was a significant lengthening of the latency of components N22, N30, P38, P 46 (Table 3).

Table 3. Indicators of latency of components of somatosensory evoked potentials of patients with vertebral pathology of lumbar spine depending on the pain

Component	Latency, ms			
	Control group n=28	Group 1 n=83	Group 2 n=46	Group 3 n=19
N22	22.1±2.2	36.2±6.1	42.1±4.9*	51.3±5.4**
N30	29.8±2.8	41.2±3.9*	49.6±4.1*	60.5±5.7**
P38	38.3±3.3	43.8±4.8	52.6±3.7*	63.9±4.2**
P46	46.4±3.2	49.1±4.0	54.3±3.4*	71.2±6.7**

Note: * – differences reliability between the indices of the control group and the group of the patients, * – $p < 0.05$, ** – $p < 0.01$

In patients with vertebral pathology with moderate and severe pain syndrome there was a significant increase in latency of components N22, N30, P38, P46, respectively, characterizing the intensification of the processes of inhibition of neural structures of the spinal cord.

Also, in patients with apparent pain syndrome there was a significant increase in the duration of intervals of absolutely all the components, indicating exhaustion and desynchronization of the higher antinociceptive centers.

As it is seen from Table 3, in patients with mild to apparent degree of pain we revealed a significant lengthening of N22 latency indices up to 42.1 ± 4.9 ms, $P < 0.05$ and 51.3 ± 5.4 ms, $P < 0.01$ (control 22.1 ± 2.2 ms); N 30 to 49.6 ± 4.1 ms, $P < 0.05$ and 60.5 ± 5.7 ms, $P < 0.01$ (control 29.8 ± 2.8 ms); P38 to 52.6 ± 3.7 ms, $P < 0.05$ and 63.9 ± 4.2 ms, $P < 0.01$ (control 38.3 ± 3.3); R46 up to 54.3 ± 3.4 ms, $P < 0.05$ and 71.2 ± 6.7 ms, $P < 0.01$ (control 38.1 ± 3.3 ms), respectively, that is characterizing the affect of fibers of peripheral sensory fibers (decrease in SSEP) of 1a-afferents of the H-reflex arc and L3-L4 afferents demyelination on a spinal level (data of SSEP study with stimulation of n. tibialis).

Thus, the idea of understanding the mechanisms of the production factors influence on the severity of clinical manifestations with pain syndrome in vertebral pathology in miners at the level of the afferent somatosensory system was enhanced in the scientific work.

CONCLUSIONS

1. Found out changes of SSEP in vertebrogenic spine pathology in miners is the criteria of the pain syndrome degree diagnostics.

2. Developed criteria for diagnosing disorders of pain sensitivity make it possible to carry out differential diagnosis of disorders in clinically ambiguous cases.

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THE IMPORTANCE OF PRENATAL DIAGNOSIS OF CONGENITAL HEART DISEASES FOR PLANNING OF DELIVERY AND POSTNATAL CARE



Elena D. Bepalova, MD
Professor, Director



Olga A. Pitirimova, MD
Obstetrician, Vice-Director



Maria N. Bartagova
Physician



Rena M. Gasanova
Cardiologist, Junior Researcher

Bakoulev Center for Cardiovascular Surgery, Moscow

INTRODUCTION

Congenital heart disease is the most common disorder of newborns, affecting one out of every 100 babies. CHD is 6 times more common than chromosomal abnormalities and 4 times more common than neural tube defects. About 25% of all infant deaths resulting are due to congenital malformations and one third of these deaths are of infants with cardiac abnormalities.

Most forms of CHD can be detected in utero, especially the severe ones with considerable fetal and postnatal morbidity and mortality. The prenatal diagnosis of major CHD requires further assessment for extracardiac (about 65%) and chromosomal (about 43%) abnormalities [1].

Fetal cardiology includes the assessment of the fetal heart for CHD and arrhythmias, the management of affected fetuses, including parental counseling for the therapeutic options, the planning of the delivery and the postnatal care.

This requires a close collaboration between obstetricians, neonatologists and pediatric cardiologists and cardiovascular surgeons.

Although there has been a great improvement in the diagnosis of CHD both prenatally and postnatally due to the availability of echocardiography. The goals of fetal echocardiography are to exclude CHD and, when present, to diagnose the specific malformations of the heart.

Echocardiography will determine whether the fetus has the type of structural abnormality and details

Abstract

Objective

Prenatal echocardiography is very important for diagnosis CHD, the management of affected fetuses, including parental counseling for the therapeutic options, the planning of the delivery and the postnatal care.

Methods

Multiple B-scan planes, Doppler color flow mapping and pulsed Doppler, 3-4 Dimensional Fetal Echocardiography. Methods of the echocardiographic identification of fetal CHD are: postnatal echocardiography, angiography, surgery, or autopsy.

Results

A total of 8619 fetal echocardiograms were obtained during the period between 2000–2010 years from which 3672 fetuses with a prenatal diagnosis of CHD were enrolled.

Conclusion

Prenatal diagnosis of major CHD was associated with improved preoperative clinical status of these infants and must include detailed extracardiac and intracardiac assessment to predict the risks of surgical treatment. Prenatal diagnosis of CHD may guide the timing and optimal location of delivery. The deliveries of patients with major cardiac anomalies in a tertiary obstetrics center close to a pediatric cardiac facility or cardiovascular surgery center allows optimal perinatal and postnatal management.

Keywords

Prenatal diagnosis, fetal echocardiography, congenital heart diseases, delivery, postnatal care.

specific CHD. This information is very important for choice of surgical repair after birth [2].

METHODS

Definition of fetal CHD was attempted from multiple scan planes including four-chamber, long- and short-axis as well as aortic arch and ductal arch views. We use 3-4 Dimensional Fetal Echocardiograms for diagnosis complex CHD after 2 dimensional echo. Optimal 3-Dimensional Fetal Echocardiograms were obtained between 22 and 27 weeks of gestation [Fig. 1, 2].

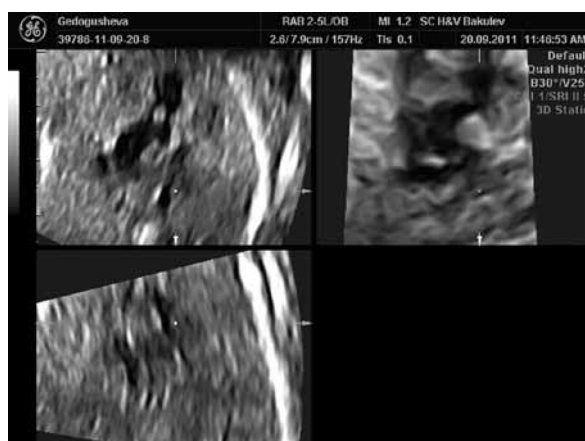


Figure 1. 3D-multiplanar reconstruction mode (FAST). Plane A: the tree-vessels view modification. Truncus arteriosus, aorta, pulmonary artery. 23 weeks gestation

3-D echocardiography enables more detailed evaluation of dynamic fetal cardiac function, but there are also technical problems with 3-D fetal echocardiograms [5,6].

Doppler color flow mapping and pulsed Doppler interrogation were used to facilitate identification of great vessel relationship, location and severity of ventricular outflow obstruction[3].

Initial fetal echocardiograms were obtained between 12 and 39 weeks of gestation (median 24.5 weeks). Major cardiac malformations should be followed serially by fetal echocardiography as progressive alterations in flow may affect growth of cardiac structures over time: for example, Very often, after prenatal diagnosis of hypoplastic left-heart syndrome (HLHS) couples have been offered termination of pregnancy

But "Termination of pregnancy should not be proposed when it is only a small left ventricle (on echo), because many of those patients end up with only coarctation of the aorta." A second echo should be carried out in these cases.

Methods of the echocardiographic identification of fetal CHD are: postnatal echocardiography, angiography, surgery, or autopsy.

The stages of Fetal Echo: The early transvaginal fetal echocardiogram at 12 to 14 weeks of pregnancy (for exclude major heart malformations for groups of risk). But early transvaginal fetal diagnosis will be repeat over 2 weeks.

The optimal transabdominal fetal echocardiogram – at 16 to 22 weeks of pregnancy. By this time, details of the fetal cardiac anatomy can be well visualized, such as the atrioventricular and ventriculoarterial connections.

Fetal echocardiographic images may be difficult after 32nd–34th weeks of gestation because of

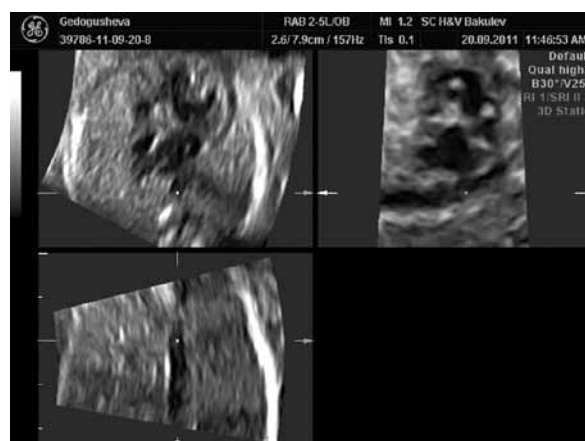


Figure 2. 3D-multiplanar reconstruction mode (FAST). Plane A: the five chamber view modification. Ventriculoseptal defect (RV – right ventricle). 23 weeks gestation

fetal rib shadowing, fetal position, or maternal body habitus.

RESULTS

A total of 8619 fetal echocardiograms were obtained during an period between 2000–2010 years from which 3672 fetuses with a prenatal diagnosis of CHD were enrolled. Here is the sample of data for three years. The number of cases is enough for statistic analyze.

CHD usually are diagnosed during the first echo.

The number of echocardiographic studies was ranging from one to four examinations. Maternal age was from 17 to 41 years old.

The stages of Fetal Echo:

- 23% of fetal echocardiograms were obtained before 18 weeks of gestation.
- 48% of fetal echocardiograms were obtained between 19–24 weeks of gestation.
- 29% of fetal echocardiograms were obtained between 25–39 weeks of gestation.

Next CHD have been diagnosed prenatally (Table 1). The most CHD are severe CHD. Outcome of prenatal diagnosis of CHD (Table 2).

Table 1. Names of CHD

Name of cardiac anomalies	N (abs.)	(%)
Atrioventricular canal (partial + complete)	15+148	6,8
Hypoplastic left heart syndrome	161	6,7
Hypoplastic right heart/tricuspid atresia	49	2,1
Conotruncal anomalies	409	17,1
Pulmonary atresia with VSD+intact ventricular septum	43+17	1,8+0,7
Isolated Ventricular septal defects	914	38,2
Coarctation of the aorta, interruption of aortic arch	57	2,4
Anomalous pulmonary venous connection	12	0,5
Congenital AV + semilunar valvar anomaly	29+34	1,2+1,4
Single ventricle	65	2,7
Potential ASD	61	2,5
Cardiac tumors	25	1,1
Congenital coronary artery anomalies, fistulae	5	0,2
Other complex cardiac anomalies	348	14,6
All	2392	100

Table 2. Outcome

Outcome	N (abs.)	(%)
The termination of pregnancy	698	29,2
Intrauterine fetal death	4	0,2
Neonatal death soon after birth	39	1,6
Fetal evolution (Small VSD)	619	25,9
Surgical repair before 1 year	604	25,2
Surgical repair after 1 year	223	9,3
Are followed up by doctors, SR is planned for the future	205	8,6
All	2392	100

The main reasons of termination of pregnancy (29,2%) are early diagnosis, a one-ventricle outcome, or multiple malformations.

Intrauterine fetal death took place about 0,2%.

The main reasons of neonatal death (1,6%) are severe CHD and multiple malformations.

Fetal evolution (25,9%). We are speaking about small muscular ventricular septal defects. Most of small ventricular septal defects are muscular VSD. This disease are the most frequent abnormalities diagnosed in utero. VSD account for 30% of all cardiac defects. Small muscular defects of the ventricular septum are subject to a high spontaneous closure rate in utero, often after 26–28 weeks of gestation, and in the first years of life.

In most liveborn infants, complete surgical repair can be achieved.

Surgical repair before 1 year were made in 25,9%. There were ductus-dependent CHD, radical correc-

tion of AVC, TF, two-forked cava-pulmonary anastomosis. Surgical repair after 1 year were made in 9,3%. There were most radical correction of Ventricular septal defects, ASD.

Are followed up by doctors, surgical repair is planned for the future in 8,6%. There were Congenital valvar anomalies, small septal defects.

MISTAKES OF PRENATAL DIAGNOSIS OF CHD

The number of mistakes of diagnosis – 81 from 2392 cases (3,4%).

The most difficult diagnosis of Truncus arteriosus and Pulmonary atresia with ventricular septal defect. It can be difficult to determine the morphology of the central pulmonary arteries and to locate the source of pulmonary blood supply [Fig.3]. It is difficult initial diagnosis of Coarctation of aorta after 34th–36th week of gestation [Fig.4].

In contrast, the prenatal diagnosis of TOF or DORV with subaortic VSD agreed in most cases with the postnatal findings.

DISCUSSION

In general, prenatal diagnosis most major CHD make results of the delivery, the postnatal care and surgical repair much better.

Fetal echocardiography has opportunity to study the most important parameters of fetal heart with major CHD for postnatal surgical repair.

Important parameters of fetal echocardiography in last weeks (32–36 weeks of gestation) are:

- Left/right ventricular diastolic dimensions in M-mode, B-mode (right-to-left ventricular disproportion: cardiomegaly, dilatation of right ventricle, right atrium or left chambers of heart; hypoplastic right or left heart);
- Atrioventricular and semilunar valves's dimensions (valve's stenosis/atresia or dilatation);
- Study of ejection fraction (Fetal heart contractility including its ability to fill and to eject blood to the body and back to the placenta);
- Inefficient of fetal circulatory (pericardial effusion, AV regurgitation, fetal non-immune hydrops, fetal arrhythmias);
- Ultrasound diagnosis of anatomical details of specific CHD.

Ultrasound details for specific CHD by the planning of the delivery and the postnatal care

Most important Ultrasound details for major CHD are:



Figure 3. 2-dimensional color Doppler image at 27 weeks gestation. The five chamber view modification. Truncus arteriosus – TA. Pulmonary artery – arrow. Aorta – Ao. Left ventricle – LV. Right ventricle – RV



Figure 4. 2-dimensional Power Doppler at 30 weeks gestation. Aortic Arch view. Coarctation of aorta – arrow

For Conotruncal anomalies:

- fetal echocardiographic definition of the great artery relationship;
- left ventricular diastolic dimension;
- dimension of foramen ovale (restrictive foramen ovale – early closure of a flap valve in the fetal heart and restriction of flow across the foramen ovale);
- dimension of ductus arteriosus [4], type of coronary arteries;
- the location of associated ventricular septal defect;
- the presence/absence of ventricular outflow tract obstruction with the other diagnostic modalities.

For Pulmonary atresia:

- the presence/absence of ventricular septal defect;
- intracardiac anatomy; presence and size of the branch pulmonary arteries;
- source of pulmonary blood supply;
- side of the aortic arch.

Hypoplastic left/ right heart:

- mitral/ tricuspid valvar anomaly (congenital parachute mitral valve, stenosis/ atresia);
- aortic valve or aortic root disease, stenosis/atresia PA, Right ventricular outflow obstruction, dimension of foramen ovale and ductus arteriosus DA.

Review of fetal evolution of CHD

Some CHD can be observed in utero. It is so interesting to prenatal diagnosis of mild Coarctation of aorta and mild valvar stenosis.

Fetal development is not affected, because of the unique fetal circulation. The large ductus arteriosus allows equalization of systolic blood pressure in the great

arteries, thus a pressure gradient does not develop in utero. But we may see dilated right ventricle resulting from increased systemic vascular resistance.

What is a program of prenatal Cardiology in our clinic?

Our program of prenatal cardiology includes:

A team of expert cardiologists trained in the evaluation and diagnosis of fetal heart problems.

What to Expect from Fetal Cardiology?

That plan will usually include:

- An accurate diagnosis;
- Prompt communication of test results to the referring health care provider;
- Tests, such as amniocentesis or magnetic resonance imaging (MRI), to look for other congenital problems;
- Directing of the Pregnancy;
- Follow-up assessments, communication and counseling (when needed);
- Close monitoring of the unborn baby's health and development;
- Careful planning of a mom's delivery that includes staying in close contact with obstetrician and cardiology doctors;
- Method of choice of delivery is natural delivery;
- Complete care of the unborn baby following delivery, with access to the cardiovascular surgery center and cardiothoracic surgery teams;
- Consultations with other services at our clinic, which may include cardiothoracic surgery, genetics and psychology services;
- Thorough and caring counseling to help couples understand the options for diagnosis, treatment and surgery;

- After delivery, the baby will be cared for at the Heart Institute. Should the newborn require surgery, our cardiothoracic surgeons can perform even the most complex surgery for congenital heart diseases.

CONCLUSION

1. Fetal cardiology is very important for diagnosis CHD, the management of affected fetuses, including parental counseling for the therapeutic options, the planning of the delivery and the postnatal care.
2. Prenatal diagnosis of major CHD was associated with improved preoperative clinical status of these infants and must include detailed extracardiac and intracardiac assessment to predict the risks of surgical treatment.
3. Prenatal diagnosis of CHD may guide the timing and optimal location of delivery. The deliveries of patients with major cardiac anomalies in a tertiary obstetrics center close to a pediatric cardiac facility or cardiovascular surgery center allows optimal perinatal and postnatal management.

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INTRODUCTION OF THE PRODUCTS REAMBERIN AND REMAKSOL FOR REDUCING TUMOR INTOXICATION AND CONCURRENT REACTIONS IN THE COMBINATION THERAPY OF OVARIAN CANCER OF THE THIRD AND FOURTH DEGREE

V.G. Cherenkov Prof., A.B. Petrov PhD, I.A. Tverezovskaya, A.A. Shpenkova PhD, T.M. Vasilyeva

*Novgorod Regional Clinical Oncologic Dispensary, Chief Medical Directorate,
Veliky Novgorod, Russia*

In most countries ovarian cancer shows the highest death rate among all gynecological tumors due to its late detection. The lethality of patients with ovarian cancer during the first year after the disease detection exceeds 35%. Over the last decade the platinum chemotherapy was able to increase the five-year survival rate after the optimum cytoreductive surgery only by 3%, from 32 to 35% [8].

As far back as the 80s a whole number of authors [3, 4] showed that patients with the most common ovarian cancer, and in particular, the one forming ascites, usually have considerable immune suppression, symptoms of anemia and intoxication. The liquid peroxidation and antioxidant blood system are inadequate [1]. The combination of ovarian cancer and old hepatitis represent an even larger problem. As a result, treatment of ovarian cancer of the third and fourth degree with high intoxication often remains unsolved in a number of aspects. It is not only necessary to look for an effective anticancer therapy but also for medicine that can reduce the tumor intoxication [2, 5, and 9].

As a rule, ovarian cancer patients of the third and fourth degree have high surgical risk. It is not possible to start with polychemotherapy for a long time, and the frequency of leukopenia increases. We have used Reamberin and, in cases of reduced kidney function, Remaksol, the main component of which is the succinic acid. Their transformation in the human body is connected to the production of energy necessary for cell activity. The capacity of this energy generation system based on the succinic acid is hundreds of times larger than that of other energy production systems. The replenishment of the pool of the Krebs cycle intermediates leads to the increase in the oxygen transport speed, decrease in the hypoxia and endotoxiosis [10].



Vyacheslav G. Cherenkov



Alexander B. Petrov

THE AIM

of the present work was to study the effectiveness of the drugs Reamberin and Remaksol for reducing intoxication and concurrent reactions which represent the main obstacle in the effective special treatment.

MATERIAL AND METHODS

The assessment of the state and degree of intoxication was carried out among 171 patients and was based on the clinical, functional and biochemical parameters before the surgery, the beginning of the polychemotherapy and 3–4 weeks after its completion according to the recommended ECOG common toxicity criteria [6].

The effectiveness of application of Reamberin (that has a direct influence on the oxidation processes in the Krebs cycle to remove intoxication and tissue hypoxia) was studied among 89 patients (age 42–79) with stage III–IV ovarian cancer with ascites after cytoreductive surgery and during their polychemotherapy according to the FIGO Stage Classification (Group 1). Retrospective patients (89) of the similar age and cancer stage were chosen as a control group

Table 1. Comparative data of the intoxication degree, reduction of blood values and status of ovarian cancer patients in the third and fourth degree before treatment

Group	Number of patients	Degree		Patient's Status (ECOG)			Intoxication degree			Degree of the reduction of blood values*			
		III	IV	II	III	IV	II	III	IV	0	I	II	III
1	89	73	16	17	48	24	16	47	26	9	35	26	19
2	82	65	17	15	42	25	13	44	25	7	32	25	18
Total	171	138	33	32	90	49	29	91	51	16	67	51	37

Table 2. Reduction rate of the haematological values before treatment and during polychemotherapy in the group with Reamberin use and in the control group

Reduction rate of hemoglobin	Group 2 (control group)		Group 1 (with Reamberin)	
	Before treatment	During the polychemotherapy	Before treatment	During the polychemotherapy
0 → 115	70	49	76	79
1 – 100 g/L-115	12	19	13	9
2- 80-100 g/L	-	10		1
3– 65-79 g/L	-	4	-	
4- < 65 g/L				
Reduction rate of white blood cells				
	Before treatment	During the polychemotherapy	Before treatment	During the polychemotherapy
9 0- >4,0 x10	72	56	81	85
1- 3,0-3,9	10	18	8	3
2- 2,0-2,9		6		1
3- 1,0-1,9		2		
4- <1,0				
Total	82	82	89	89

(Group 2). These 89 patients were operated on in the Novgorod regional clinical oncologic dispensary and city hospitals without the application of Reamberin. Remaksol was used for 9 patients with toxic hepatitis during 5 days until the normalization of parameters.

Even the optimal cytoreductive surgery doesn't stop the disease from growing if the adjuvant polychemotherapy is not carried out in time.

The platinum, cyclophosphamide and/or doxorubicine drugs (a strict one-day combination of cisplatin and cyclophosphamide, or cisplatin, doxorubicine and cyclophosphamide) are used as standard treatment methods in the polychemotherapy. These drugs, besides being highly effective, are also nephro- und cardiotoxic, which has to be taken into consideration. In case the anemia values were lower than 100 g/L, the preparation for the polychemotherapy always started with hemotransfusion.

Table 3. Rate of the heart dysfunction before treatment and during polychemotherapy in the group with Reamberin use and in the control group

Rate of the heart dysfunction	Control group		Group 1	
	Before treatment	During the polychemotherapy	Before treatment	During the polychemotherapy
0 – no dysfunction	20	7	18	23
1 – clinically unsuspected dysfunction	19	20	21	21
2 – transient symptomatic dysfunction, treatment necessary	26	32	27	23
3 – correctable dysfunction, rhythm disturbance	17	23	23	22
Total	82	82	89	89

Reamberin, based on the succinic acid, is dissociated under physiological conditions and is called succinate. The capacity of the energy generation system based on the succinic acid is hundreds of times larger than that of other energy production systems. The replenishment of the pool of the Krebs cycle intermediates leads to the increase in the oxygen transport speed, decrease in the hypoxia and endotoxiosis [9].

Reamberin was injected intravenously as a 1,5% solution 1–2 days before the surgery, every day after the surgery (no more than 90 drops per minute during 5–10 days, 400 ml per day) and during each course of polychemotherapy three days in a row (before, on the day of and the day after the polychemotherapy).

The postsurgical polychemotherapy was carried out in both groups in the following combinations: cyclophosphan 750 mg/m² + cisplatin 75 mg/m² or cisplatin 50 mg/m² + cyclophosphan 500 mg/m² + doxorubicine 50 mg/m² every three weeks with pre- and posthydration, up to 2–4 liters.

For the control group, the number of anemia and leukopenia of the first degree cases before the polychemotherapy was 12 (14,6±2,1%) and 10 (12,2±0,9%),

correspondingly. During the therapy the values of anemia and leukopenia, including stage II–III, increased up to 33 ($40,2 \pm 3,6\%$) and 26 ($31,7 \pm 3,2\%$), accordingly. The values in Group 1 (with Reamberin) before the treatment were 13 ($14,6 \pm 2,1\%$) and 8 ($8,9 \pm 0,5\%$) correspondingly, and during the polychemotherapy the haematological values practically remained unchanged (anemia of stage I–II – $11,2 \pm 1,1\%$ and leukopenia – $4,4 \pm 1,6\%$). The difference in the number of cases and the reduction rate of hemoglobin and white blood cells in the test group in comparison to the control group is statistically reliable ($p < 0,01$).

The rate of the heart dysfunction of stage II–III in Group 1 was observed among 50 patients ($56,1 \pm 3,7\%$) before treatment. With the help of Reamberin the full polychemotherapy treatment was carried out, and the frequency of heart dysfunction was reduced to 45 ($50,56 \pm 3,4\%$).

The control group with patients having some heart dysfunction of stage II–III showed quite the opposite result during the polychemotherapy: the number increased from 52, $4 \pm 3,4\%$ (43 patients) to 67, $1 \pm 4,1\%$ (55 patients), there was a necessity of additional therapy, extension of the period between the polychemotherapy courses or a decrease in drugs. The difference in comparison to the control group is statistically reliable ($p < 0,05$).

One of the parameters for assessing the level of the urinary system disorder is the increase rate of creatinine. The increase rate of creatinine of the first degree (Table 4) is relatively the same for the patients in Group 1 (12 patients – $13,5\%$) and Group 2 (11 patients – $13,4\%$).

Only three patients ($3,37\%$) from Group 1 among those being treated with Reamberin before and during the polychemotherapy showed the same increase in the creatinine level. The number of patients with the increased creatinine level (degree I–III) in the control group grew to 34 ($41,4\%$), which in 12 cases ($14,6\%$) resulted in the suspension of the chemotherapy and additional therapy. The difference between the groups is statistically reliable ($p < 0,001$).

Here are some other manifestations of the toxicity among the ovarian cancer patients treated with Reamberin: nausea and vomiting of degree I–II was observed among 24 patients ($26,9 \pm 2,2\%$) and was mainly delayed. The corresponding number of patients in the control group (degree II–III) was 45 ($59,2 \pm 3,4\%$), 28 of which had acute symptoms (24 hours after the beginning of the chemotherapy) in spite of the fact that 30 minutes before the beginning of the chemotherapy all patients received an intravenous injection of antiemetic drugs (ondancetron 8 mg or granisetron 1 mg).

The dynamics of the postsurgical levels of serum CA-125 (high-molecular glycoprotein that normally doesn't exceed 35 units/ml) before and during the

Table 4. Increase rate of creatinine before treatment and during polychemotherapy in the group with Reamberin use and in the control group

Increase rate of creatinine	Group 2 (control group)		Group 1 (with Reamberin)	
	Before treatment	During the polychemotherapy	Before treatment	During the polychemotherapy
0 – no disorder (upper limit)	71	48	77	88
1 – <1,5 times over the upper limits	11	21	12	2
2 – 1,5-3,0 times over the upper limits	-	11	-	1
3 – 3,1-6,0 times over the upper limits	-	2	-	-
Total	82	82	89	89

Table 5. Dynamics of postsurgical levels of serum CA-125 during polychemotherapy in both groups

Group	Ca-125 level (units/ml)						
	1000 >	500–1000	300–500	100–300	35–100	<35	
After surgery	1	2	3	14	31	39	-
	2	5	8	19	37	13	-
After the 2nd course	1		-	2	19	57	11
	2		6	12	38	23	3
After the 4th course	1			-	5	50	34
	2			7	24	38	13
After the 6th course	1					11	78
	2				16	39	27

polychemotherapy has also been researched. According to N.S. Sergeyeva and co-writers (2002), it is an objective predictive factor of the effectiveness of the ovarian cancer treatment. According to the majority of writers, the level doesn't so much depend on the volume of the tumor as on the involvement of the peritoneal mesothelioma.

After the second course of the polychemotherapy with the combination of cyclophosphan+cisplatin or cyclophosphan+doxorubicine+cisplatin the level of the CA-125 was higher than 100 units/ml among the majority of patients, 59 ($68,2 \pm 4,2\%$), in the control group and only among 21 patients ($23,5 \pm 1,9\%$) in Group 1, which is twice as low than in the control group.

After the fourth course the level of less than 35 units/ml reached the norm among $38,2 \pm 2,4\%$ of patients in Group 1, and was lower than that only among 13 patients ($17,1 \pm 0,94\%$) in Group 2.

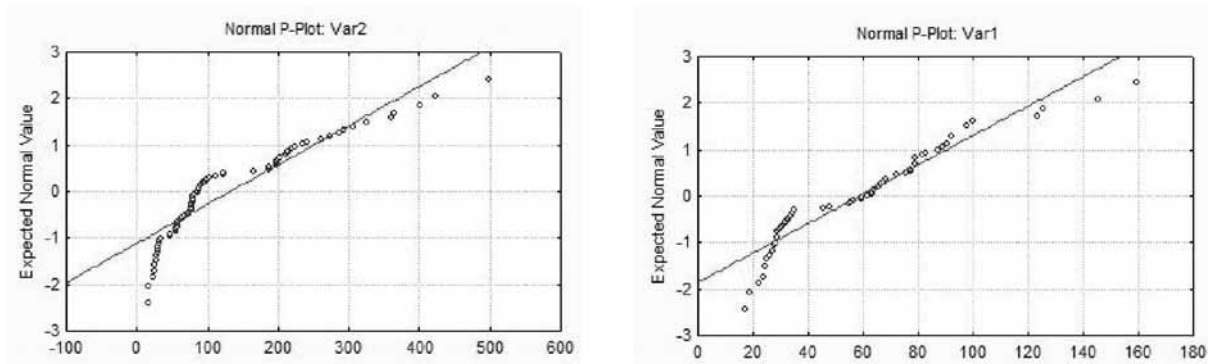


Fig. 1. Comparative data of the disperse analysis of the tumor marker CA-125 after the 4th course of the polychemotherapy in the test group with Reamberin (var. 1) and the control group (var. 2)

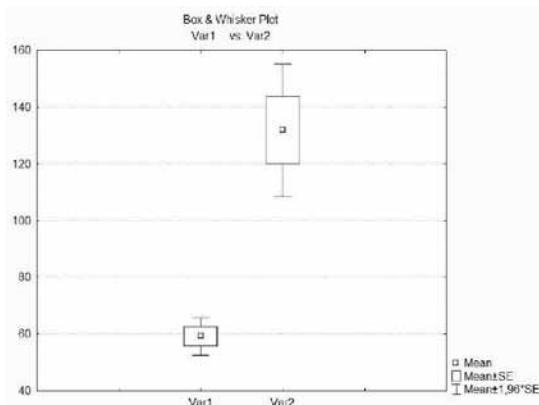


Fig. 2. Levels of the tumor marker CA-125 in Group 1 (var. 1) in comparison to the control group (var. 2)

The statistical analysis of the research results was carried out in the SYS system (Statistical Analysis System, SAS Institute Inc., USA) with the application of the standard algorithms of the variation statistics and in the program STATISTICA 8.0.

The analysis showed that the effects of the decrease in the CA-125 after the second, fourth and sixth course are at level $p < 0.05$.

Thus, the research in the application of the 1.5% solution of Reamberin before and after the cytoreductive surgery and during the following polychemotherapy has shown that Reamberin is a drug that reduces intoxication and side effects of the special ovarian cancer treatment without reducing the anti-tumor effect.

CONCLUSION

1. Application of Reamberin before cytoreductive surgery and during one-day (strict) courses of polychemotherapy creates conditions for reducing tumor intoxication and anemia.
2. Reamberin and Remaksol prevent toxicity during polychemotherapy (using platinum- and doxorubicine-based drugs) without reducing the anti-tumor effect.

3. The decrease in the tumor marker CA-125 is registered within a shorter period of time than in the control group. The statistical analysis shows that the effects of the decrease in the CA-125 after the second, fourth and sixth course are significant at level $p < 0.05$.

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KARTALIN – AGENT OF YOUR CHOICE IN THE TOPICAL TREATMENT OF CHRONIC DERMATOSIS

V.S. Dmitruk

Siberian State Medical University of Tomsk

Abstract

Correct choice of topical treatment in treating chronic dermatosis is a fundamental issue facing dermatologists, and in most cases is the most important factor for achieving long-term remission. A study on the clinical effectiveness of Kartalin ointment was conducted at the skin disease clinic of the Siberian State Medical University. As a result of a comprehensive treatment including the use of Kartalin, good therapeutic effect, as evidenced by improved PASI and SCORAD scores, was observed in 100 psoriasis sufferers and 46 persons diagnosed with atopic dermatitis.

Keywords

kartalin, psoriasis, atopic dermatitis.

INTRODUCTION

Psoriasis and atopic dermatitis are types of dermatosis that have attracted the interest of a great deal of scientific researchers. Nevertheless, its pathogenesis is not fully understood [2, 3, 8, 10]. Given the high percentage of the population suffering from this skin condition, systemically effective topical pharmaceuticals are actively sought and employed, especially those restoring keratinocyte proliferation and differentiation processes, thus normalizing the structure and functional capability of the epidermis [1, 4, 5].

The first step in the topical treatment of such diseases is the use of anti-inflammatory and immunosuppressant products, primarily topical corticosteroids [6, 9].

As a result of the hyperkeratosis and parakeratosis occurring in psoriasis and atopic dermatitis, epidermis barrier function is impaired by decreased skin moisture and degraded stratum corneum integrity due to a decrease in quantity of fortifying lipidic substances (cholesterol, fatty acids, triglycerides) [11, 12]. In light of the above, psoriasis and atopic dermatitis therapies make extensive use of substances that moisturize and “oil” the skin.

Lipids (fatty acids, triglycerides, phospholipids, cholesterol) serve as the primary means of regulating transepidermic water loss. Dermatology currently makes widespread use of cosmetics that include the above substances. For patients with chronic dermatological conditions, it can take anywhere from a week to



Vadim S. Dmitruk

Associate Professor, Department of Dermatology & Venereology

several months for pathologically changed skin to heal, and thus the cumulative cost of procuring the aforementioned substances over a course of treatment may range from dozens to hundreds of dollars.

There is a good Russian-made alternative to the above barrier-function restoring substances: Kartalin ointment (Certificate of Conformity No. 7147870). This substance falls in the “solid-oil” category of ointment (like Rybakov ointment, etc.), which has been used for at least a decade to treat chronic skin conditions [7].

In consideration of the above, our study aim was to evaluate the clinical effectiveness of Kartalin for patients with atopic dermatitis and psoriasis.

METHODS AND MATERIALS

In order to achieve the study aim, 100 patients diagnosed with psoriasis were examined and treated at the Siberian State Medical University Skin Disease Clinic. Initial PASI index scores were calculated for all patients under our observation on the basis of their clinicopathologic states. Patients with mild to moderate psoriasis (up to 50 points on the PASI index) were selected in the study group. PASI index scores were recalculated after 4 weeks and treatment effectiveness was evaluated based on this data.

The first study group – Group A (n=50) – received standard inpatient treatment consisting of: Disintoxicating solutions, hyposensitizing agents, and vitamins coupled with daily application of Kartalin ointment on psoriatic papules over the course of 4 weeks.

The second group – Group B (n=50) – received 4 weeks of comprehensive inpatient treatment comprising disintoxifying and hyposensitizing agents, vitamins, indifferent ointments, and therapeutic skin care products.

The initial PASI score for group A was 32.6 points. The initial psoriasis severity indicator (PASI) for group B was 31.4 points (figure 1).

PASI scores for the study groups were calculated again at the end of treatment (after 4 weeks) in order to provide a window into the psoriasis symptom regression trend. Group A now scored at 13.1, and Group B at 18.6.

It is apparent from figure 1 that negation of clinical psoriasis symptoms will occur in both study groups over the course of treatment. After 4 weeks, a PASI score reduction was observed in every patient treated. Meanwhile, it fell by 59.8% in Group A and 40.8% in Group B. The PASI score improvement trend in both groups makes it possible to state that a clinical improvement will occur in Group A after administered therapy (a PASI score improvement of more than 50%).

The second part of the study consisted of observing and treating 46 patients with atopic dermatitis. Criteria for inclusion in the group were: Clinically confirmed diagnosis, patient informed consent, having reached adolescence or adulthood, and clinical lichenoid dermatitis or squamous dermatitis with lichenification. Criteria for exclusion from the study groups were: Diffuse atopic dermatitis, a severe case, infant or childhood age, individual intolerance for ointment ingredients, or pyogenic complications.

The patients were divided into two groups. The first group – Group C (n=26) – comprised patients who had received topical treatment in the form of Kartalin ointment over the course of 2 months. The second group – Group D (n=20) – comprised patients receiving topical treatment consisting of both indifferent and moisturizing ointments, as well as cosmeceuticals. The SCORAD index was used to determine atopic dermatitis severity. At the beginning of the course of treatment, SCORAD scores were: 59 points for the first group – Group C – and 60 points for Group D, the second group. After the course of treatment, that indicator improved to 14 points for Group C, and 18 points for Group D (figure 2).

All of the study groups were representative in terms of age, sex, and length of time having suffered from psoriasis. Data was statistically analyzed using the Biostastica 4.03 software package (1998). Mathematical analysis of the data was undertaken using Student's criteria. Differences were considered statistically significant at $p < 0.05$.

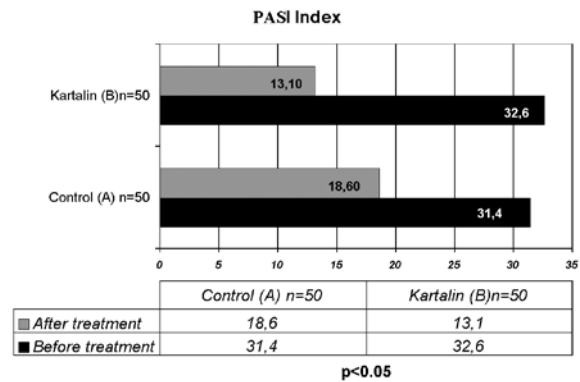


Figure 1.

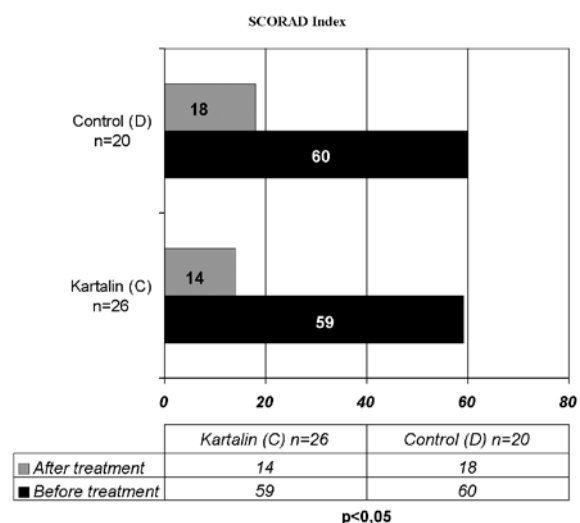


Figure 2.

CONCLUSIONS

In view of the above, the following conclusions may be drawn:

1. Kartalin is effective in the topical treatment of atopic dermatitis (lowering SCORAD scores by 76%) and may be used in single-agent treatment of mild and moderate atopic dermatitis with squamous symptoms and lichenification in inpatient and outpatient settings.
2. Kartalin ointment is an effective product in the topical treatment of psoriasis (reducing PASI scores by 59.8%) and may be effectively used in the comprehensive treatment of mild and moderate psoriasis.

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MORPHOLOGY OF BLOOD SERUM IN ACUTE PANCREATITIS

V.G. Firsova MD Ph.D, Ju.P. Potekhina, V.V. Parshikov

Nizhny Novgorod State Medical Academy, Municipal Hospital No. 35,
Nizhny Novgorod, Russia



Victoria G. Firsova

INTRODUCTION

Acute pancreatitis (AP) is a widespread and severe disease in abdominal surgery. An early development of systemic inflammatory response causing a multiple organ dysfunction syndrome (MODS) plays a particular role in its pathogenesis [1, 2]. A lot of researches show the lack of a significant breakthrough in the surgical management of AP [3, 4]. Probably, the

future in the mortality decrease belongs to the medical treatment aimed at discontinuing pathological reactions cascade including impact on nuclear factors of cytokines synthesis [5, 6]. In this connection, it is very important to identify the patients with severe necrotizing AP (PN) in the course of first 24 hours to realize the whole complex of intensive therapy. Currently, several factors are used for early prediction of severe AP, prognostic evaluation of different stages and development of complications. They include clinical features, markers of pancreatic injury and markers of inflammatory response [7]. Multifactorial scoring systems such as Ranson, Glasgow, Imrie, APACHE II and clinico-biochemical systems have similar accuracy after 48 h of admission. Their use for early diagnostics is limited [8, 9]. Different serum markers (IL-1 β , IL-6, IL-8, TNF- α , trypsinogen-2 and trypsin-2-alpha-1-antitrypsin, serum amyloid A, neopterin, metalloproteinases-2, -9, serine proteinase and others) have a high sensitivity and predictive value for severe PN, but are not clinically applicable [10, 11, 12]. Currently, C-reactive peptide is the only marker applied routinely in hospitals. Its peak serum concentration is achieved in 72 h. Thus, the use of this acute phase protein to differentiate interstitial pancreatitis (IP) and PN within first 24 hours is acceptable not in all the cases. The relationship between AP severity and pancreatic necrosis size is postulated by the majority of researchers [13, 14]. Pancreatic necrosis forms in the period of 24–72 hours from the disease onset. A zone of destruction could

Abstract

Introduction

The problem of early diagnostics and prognosis of severe acute pancreatitis (AP) has not solved yet. Multifactorial scoring systems are good predictors of pancreatic necrosis and its severity. They have similar accuracy, but consume 48 hours for the full assessment. Inflammatory markers are not widely available. The distinction between interstitial and necrotizing pancreatitis by contrast enhanced CT scan can be reliably made after 2–3 days of hospitalization. The study was performed to clarify the morphological changes in blood serum in different course of AP and how it can help in its prognosis.

Patients and methods

There were examined 51 patients with AP treated in Hospital №35 in Nizhny Novgorod in 2009–2010. They were grouped according to Atlanta classification. Group 1 (n=24) – cases of necrotizing pancreatitis, group 2 (n=37) – interstitial pancreatitis. Blood samples were taken on admission, 12 h after admission, and every 24 h within first 3 days and further in different periods in the course of the disease. Serum specimens were dried in standard conditions and then examined by means of light microscopy.

Results

There was found a meshwork in the peripheral zone of dried serum specimens in all cases of severe AP with lethal outcome (n=4). Crystal structures in form of dendrites were observed in central area in 16 patients with necrotizing pancreatitis and in 2 – with interstitial form (p=0.0003). The hyperpigmentation in the boundary zone was seen in all cases. There was a weak correlation between severity of AP and intensity of hyperpigmentation (r=0.31; p=0.024). The mentioned phenomenon was particularly marked in biliary pancreatitis. Arnold's structures were in the peripheral zone in both groups, but only in 3 patients with severe AP and multiple organ failure.

Conclusions

AP causes marked changes in biochemical status of the body that are reflected in morphological picture of blood serum. The presence of crystal structures in central area of dried serum specimen is indicative of high probability of necrotizing pancreatitis. A meshwork in the peripheral zone is associated with a severe AP and poor prognosis. Arnold's structures are a positive sign of localization of the inflammatory process.

Keywords

Acute pancreatitis, Prognosis, Early diagnostics, Morphology of blood serum

be correctly evaluated by contrast-enhanced CT and ultrasonography in these periods. On the other hand, multiple organ failure develops in approximately 10% of patients with IP [15]. At present, the problem of early diagnostics of severe AP is not considered to be solved. The morphology of blood serum in AP is of great interest when estimating pathological changes in homeostasis in their unity. Recently the notion "morphology" in biology has been referred only to cell tissues while biological fluids have not been included into morphology research. In the study there was used a method of wedge-shape dehydration developed by Shabalin V.N., Shatokhina S.N. [16], which makes it possible to analyze morphological structure of blood serum. Using the mentioned method of dehydration of a drop of blood serum, a very thin film (facia) is obtained that is actually a fixed "section" of the studied fluid. The process of dehydration has a phase character because of unequal drop thickness in the center and periphery, the difference in osmotic and oncotic forces. The facia structure presents an integrated figure of all existing in biological fluid complex molecular interconnections that are regulated and transformed onto macroscopic level in a special way. The facia of blood serum in physiological status of organism is characterized by zonality, symmetric localization of radial fissures, right-angled and round elements. The objectives of the study were to clarify the morphological changes in blood serum indifferent course of AP and how it can help in its prognosis.

PATIENTS AND METHODS

51 patients with AP were treated in Hospital №35 in Nizhny Novgorod in 2009–2010. They were grouped according to Atlanta classification. Group 1 ($n=24$) – PN cases, group 2 ($n=37$) – IP. There were 25 patients with severe AP and 26 – with a mild form of the disease. Pancreatic necrosis was verified by ultrasonography, contrast-enhanced CT, magnetic resonance imaging, histological analysis and intraoperatively. Blood samples were taken on admission, 12 h after admission, in 24 h intervals within first 3 days and further in different periods in the course of the disease. A drop of blood serum ($V=20$ mcl) was dried on the slide at 20°C , relative humidity 65% and minimal air flow. The duration of drying was 3 h. The investigation of structural elements of blood serum was made by means of light microscopy. The comparison of two independent groups was carried out using Mann-Whitney U test. Spearman rank was determined for the purpose of correlation analysis.

RESULTS

The investigation of blood serum morphology revealed a number of phenomena, occurrence and

intensity of which differed in mild and severe AP. There was found a meshwork in the peripheral zone of dried serum specimens in all cases of severe AP with lethal outcome ($n=4$) (Fig. 1). The sign was seen on the first day of the disease and remained till the death of the patient in spite of multi-component intravenous medication. Similar changes in the peripheral zone were observed in other two patients with NP who survived, but the course of the disease was accompanied by MODS, pancreatic abscesses, fistulas formation. The development of complications was the cause of reoperations and a prolonged stay in an intensive care unit. The finding of the meshwork in survived patients was non-persistent. Crystal structures in the form of dendrites branching at an angle $60-90^{\circ}$ were observed in central area in 16 patients with PN both with and without MODS and in 2 – with interstitial form (Fig. 2). The groups differed significantly regarding the presence of the sign ($p=0.0003$) (Fig. 3, 4). The evolution of appearance or disappearance of such crystals reflected different periods in the course of AP: clinical improvement, MODS reduction, the decrease of intoxication or complications development. The sign was continuously revealed in blood specimens in the cases with lethal outcome (Fig. 5, 6). The hyperpigmentation in the boundary zone was seen in all patients (Fig. 7). There was a weak correlation between severity of AP and intensity of hyperpigmentation ($r=0.31$; $p=0.024$). The mentioned phenomenon was particularly marked in biliary pancreatitis and chronic alcoholism. An infusion therapy led to the disappearance of hyperpigmentation within 1-2 days or the decrease in its intensity (Fig. 7, 8). In PN the present sign persisted during 5–10 days, in several cases – longer time. Crescent formations were seen in the peripheral zone in 13 patients, and only in 3 of them with PN (Fig. 9). These formations were difficult to identify in the presence of meshwork, haemolysis. Thus, they could not be estimated in quite a number of patients. Arnold's structures were in the peripheral zone in 23 persons: 11 of group 1 and 12 of group 2, but only in 3 patients with severe AP and MODS (Fig. 10). Arnold's structures were more expressed in cases of pancreatic infiltrate.

DISCUSSION

Pathogenesis of AP presents a cascading process, which is poorly understood especially on the molecular level. Inappropriate intracellular activation of proteolytic enzymes and their inflow in interstitium causes cytokines reactions [17]. The substances produced by polymorphonuclear leucocytes and other cells under the influence of cytokines damage phospholipid membranes not only in pancreatic tissue, but in

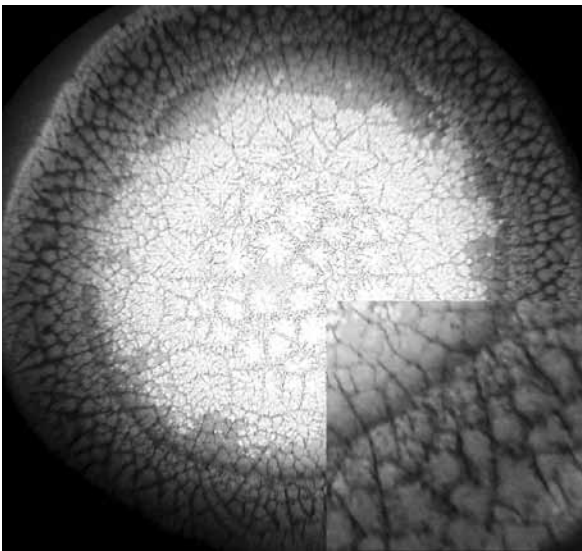


Fig.1. Meshwork in the peripheral zone

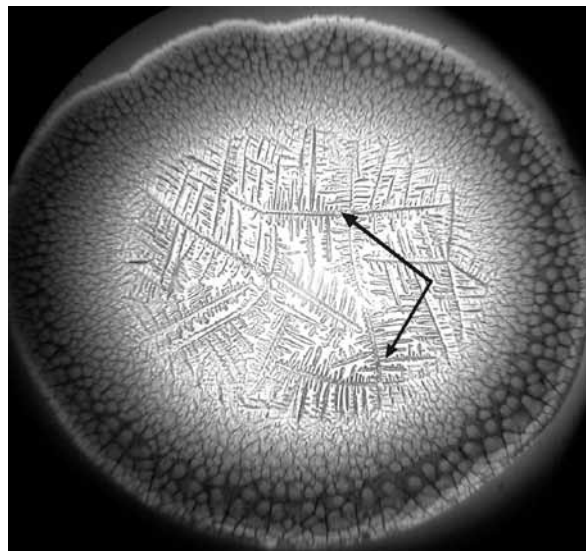


Fig. 2. Crystal structures in central area in PN

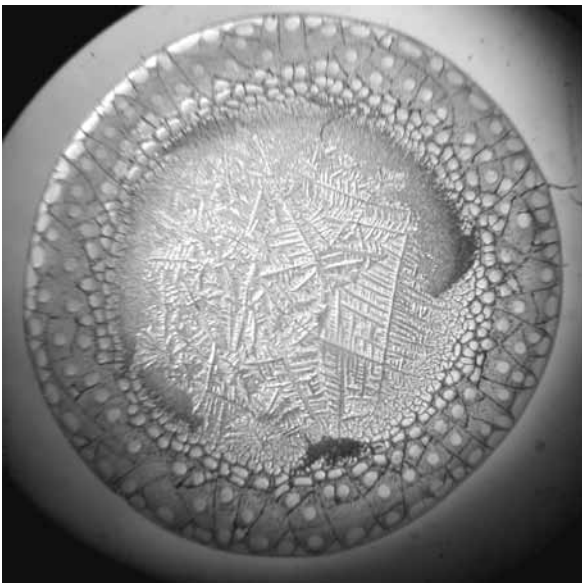


Fig. 3. Crystal structures in central area in PN, third day of the disease

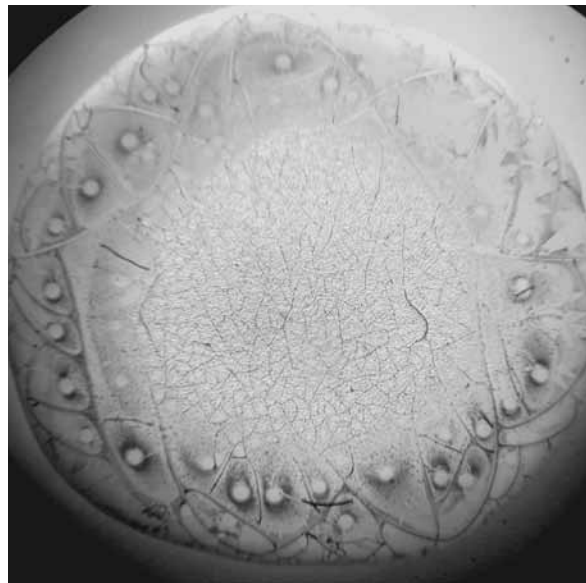


Fig. 4. Structureless central area in IP, the third day of the disease

different organs [18, 19]. Owing to this, the products of cells degradation, inflammatory mediators, lipid peroxides come in blood. All these factors together with hypoxia, acidosis and energy deficiency lead to deep disturbances in homeostasis [20]. The function of blood proteins is altered, that is reflected in serum's structure formation. Particularly the coupling capacity of albumins decreases to a considerable extent [21, 22, 23]. Albumins were shown to localize in the peripheral zone by wedge-shape dehydration of blood serum [24]. As a result of albumins conformation, changes in the number and form of fissures of dried serum specimen occur [25]. The meshwork observed in patients

with extremely severe course of AP and lethal outcome can be an evidence of significant abnormalities in the structure and function of albumins due to endotoxemia. The detection of the sign mentioned is considered to be prognostically unfavorable. The other aspect of changes in molecular interactions in blood serum is crystal structures formation in central area. A crystal form is known to be determined much by the elements of environment, i.e. by other dissolved organic and mineral substances. A type of crystallization correlates with the severity of pathology [16]. Basic crystal types could be seen in healthy subjects by means of polarization microscopy or in dark background with

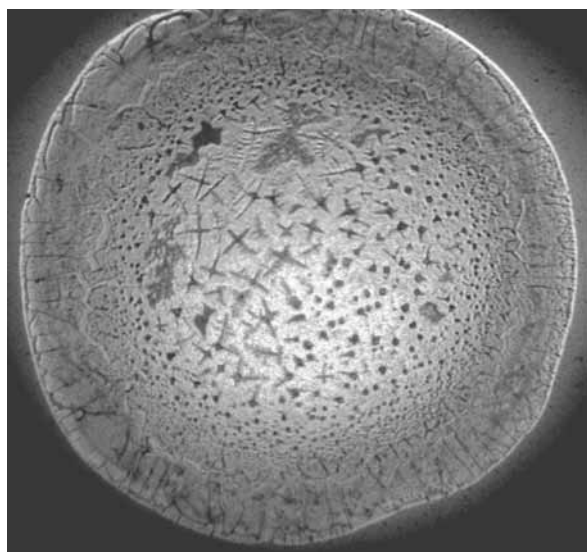


Fig. 5. Crystal structures in PN, lethal outcome, the fifth day of the disease

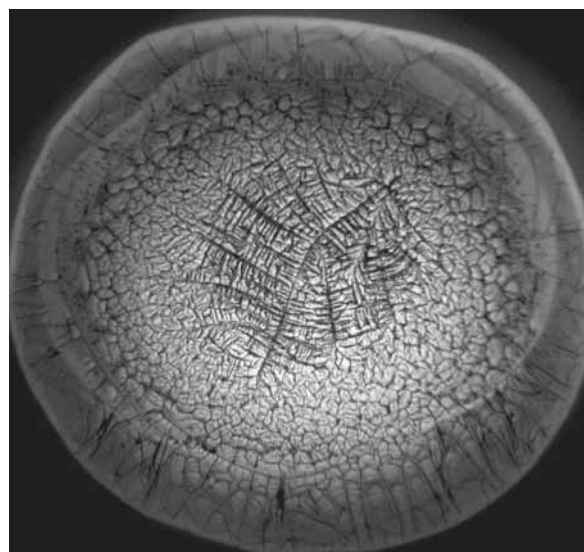


Fig. 6. Crystal structures in PN, lethal outcome, the seventh day of the disease

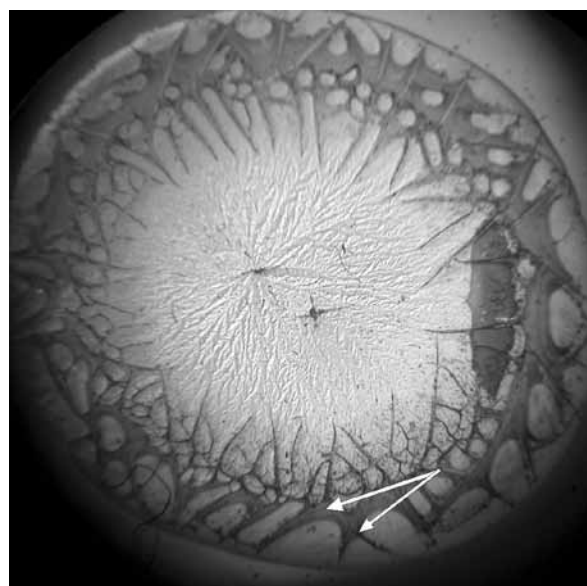


Fig. 7. Hyperpigmentation in the boundary zone, the third day of the disease

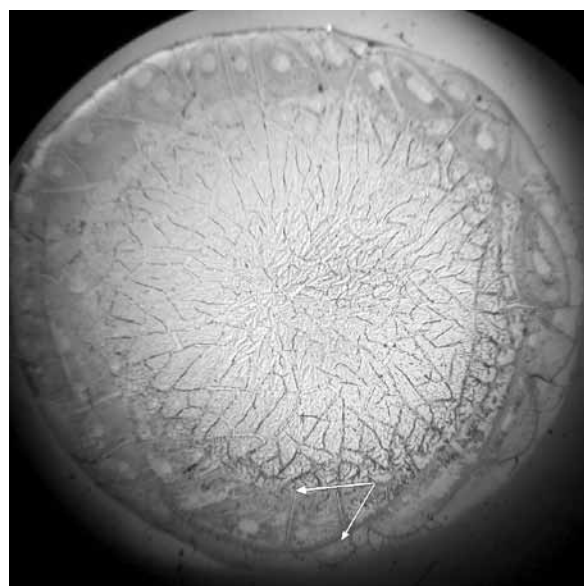


Fig. 8. Decrease of hyperpigmentation in the boundary zone, the sixth day of the disease, the same patient

lens magnification $\times 100$. Crystals revealed were large (up to 0.5 mm), clear distinguishable even with lens magnification $\times 25$ or less. We suggest the formation of such structures to be due to the imbalance between saline and organic components of serum, especially marked in severe PN. In both groups there was seen hyperpigmentation in the boundary zone, where globulin fraction localizes. The majority of acute phase proteins belong to globulins, the synthesis of which is carried out in the liver. In the course of the research there was not found a strong correlation between hyperpig-

mentation intensity and AP severity. However, acute phase proteins concentration does not always reflect PN severity [3]. On the other side, liver function alters more and earlier in individuals with chronic alcohol abuse and biliary etiology of AP that can influence the hyperpigmentation appearance. Crescent formations were found in 13 patients from 51 and in view of the fact, that it could be difficult to identify in quite a few cases, its diagnostic significance was not determined in our investigation. Arnold's structures were described in acute and chronic inflammatory processes including

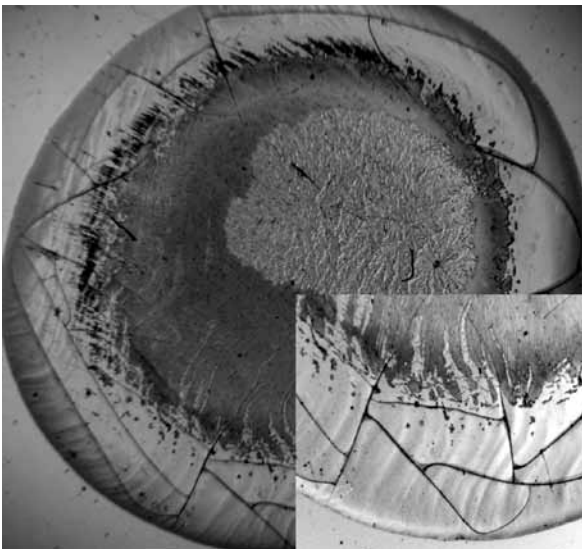


Fig. 9. Crescent formations in the peripheral zone

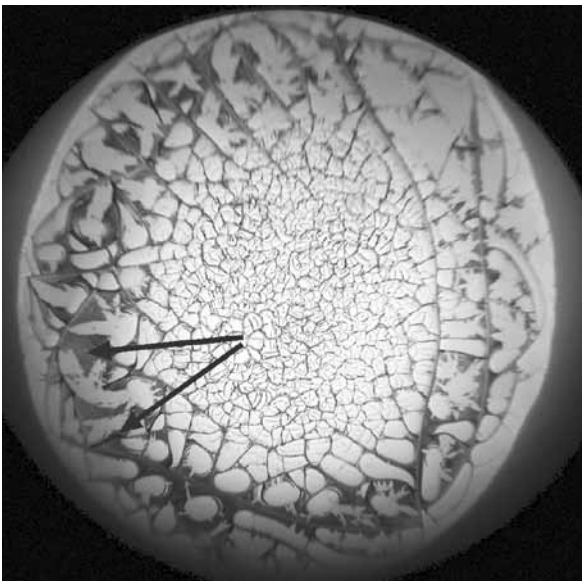


Fig. 10. Arnold's structures in the peripheral zone

infectious diseases, sepsis [26]. Such structures were found both in group 1 and group 2. In severe AP this marker was observed only in 3 persons and in no case of lethal outcome. On the contrary, in favorable course of PN, infiltrate formation and localization of inflammation, Arnold's structures were clearly expressed. It enables to consider Arnold's structures as a certain positive sign of anti-inflammatory mechanisms competence. Phenomena revealed in dried blood serum in AP have no well-defined explanation physically. However, their connection with AP course is apparent.

The latter fact is confirmed by analysis of blood serum in different periods of the disease during the treatment.

CONCLUSION

Deep disturbances in homeostasis in AP are reflected in morphological picture of blood serum. Revealed markers have no specificity relative to AP, but characterize the degree of pathological changes. The presence of crystal structures in central area of dried serum specimen indicates a high probability of PN. A meshwork in the peripheral zone is associated with severe AP and poor prognosis. The maintenance of mentioned signs in series of tests is the most unfavorable. Arnold's structures are positive signs of localization of the inflammatory process. Thus, the investigation of blood serum by means of wedge-shape dehydration makes it possible to determine the severity of AP and predict the outcome in some cases. The method is available in any hospital.

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MODERNE BEHANDLUNG DES MAGENKARZINOMS

Prof. Dr. Guido Schumacher

Klinik für Allgemein-, und Viszeralchirurgie; Städtisches Klinikum Braunschweig, Deutschland

EINLEITUNG

Bösartige Tumoren des Magens (Magenkrebs, Magenkarzinom) entwickeln sich meist in der Magenschleimhaut. Sie gehen zu 95 Prozent vom Drüsengewebe aus. Man spricht daher auch von Adenokarzinomen. Magenkrebs gehört in Deutschland zu den häufigsten bösartigen Erkrankungen. Nach Schätzungen des Robert-Koch-Instituts erkrankten im Jahr 2000 11.107 Männer und 9.865 Frauen an dieser Krebsart. Obwohl Magenkrebs in den Westlichen Industriestaaten an Häufigkeit stetig abnimmt, stellt er in Deutschland immer noch die fünfthäufigste Tumorerkrankung bei beiden Geschlechtern dar. Ebenso gehört Magenkrebs noch immer zu den häufigsten tumorbedingten Todesursachen. Das hängt insbesondere damit zusammen, dass Magenkrebs meist zu spät erkannt wird. Die Aussicht auf Heilung ist dann gering. Nach Angaben des Statistischen Bundesamtes verstarben 1999 in Deutschland 6.902 Männer und 6.243 Frauen an dieser Krebsart.

Magenkarzinome sind Tumoren, die im Magen zwischen der Kardia und dem Pylorus entstehen. Die genaue Lokalisation entscheidet über die Operation. Hierbei wird meist eine komplette Gastrektomie durchgeführt. In Einzelfällen kann eine subtotale Magenresektion erfolgen. Welche Operationstechnik verwendet wird, hängt von mehreren Faktoren ab, die im folgenden Text erläutert werden.

URSACHE UND RISIKOFAKTOREN

Die Ursachen für die Entstehung von Magenkrebs sind bisher nicht vollständig geklärt. Man kennt jedoch bestimmte Faktoren, die das Risiko, an Magenkrebs zu erkranken, erhöhen. So spielen, neben einer gewissen erblichen Veranlagung, Ernährungsfaktoren eine bedeutende Rolle. Darüber hinaus können eine Infektion mit dem Bakterium *Helicobacter pylori* sowie verschiedene Vorerkrankungen des Magens das Risiko einer Krebserkrankung erhöhen. Auch Rauchen hat einen Einfluss auf die Entstehung von Magenkrebs. Folgende Faktoren erhöhen das Magenkrebsrisiko:

Ernährung

Ernährungsgewohnheiten spielen eine wichtige Rolle bei der Entstehung von Magenkrebs. Insbeson-



Klinik für Allgemein-, und Viszeralchirurgie
Städtisches Klinikum Braunschweig
Salzdahlumer Strasse 90
38126 Braunschweig
g.schumacher@klinikum-braunschweig.de

dere der häufige Verzehr stark gesalzener Speisen und ein geringer Genuss von frischem Gemüse und Obst sind als Risikofaktoren belegt. Des Weiteren scheinen gepökelte, gegrillte und geräucherte Speisen das Auftreten von Magenkrebs zu fördern. Beim Räuchern und Grillen entstehen Krebs erregende Substanzen (Kanzerogene) durch unvollständige Verbrennung. Beim Pökeln von Fleischwaren werden Nitrat- und Nitratsalze verwendet, die beim Erwärmen oder im Magen Nitrosamine bilden. Nitrosamine sind ebenfalls sehr starke Kanzerogene. Auch Gifte, die von Schimmelpilzen gebildet werden (Aflatoxine), wirken Krebs erregend. Der erwähnte Rückgang der Erkrankungszahlen in den vergangenen zwanzig Jahren ist wahrscheinlich besonders auf die veränderten Ernährungsgewohnheiten zurückzuführen: Durch die allgemeine Verbreitung von Kühl- und Gefrierschränken und die verbesserte Versorgung mit frischem Obst und Gemüse sind Konservierungsmethoden wie das Salzen, Pökeln oder Räuchern in den Hintergrund getreten.

Infektionen

Als weiterer Risikofaktor gelten Entzündungen der Magenschleimhaut, die durch das Bakterium *Helicobacter pylori* ausgelöst werden. Eine Infektion mit diesem Erreger führt zu einer Risikoerhöhung für Magenkrebs.

Vorerkrankungen des Magens

Verschiedene Vorerkrankungen des Magens können mit einem erhöhten Risiko für Magenkrebs einhergehen. Ein erhöhtes Krankheitsrisiko liegt zum Beispiel dann vor, wenn Sie an einer chronischen Magenschleimhautentzündung (chronisch-atrophische

Gastritis) leiden. Diese kann unter anderem durch das Bakterium *Helicobacter pylori* hervorgerufen werden.

Auch Patienten, die an Magenpolypen – also gutartigen Wucherungen der Magenschleimhaut – sowie an einer bestimmten Form der Blutarmut („perniziöse Anämie“ aufgrund von Vitamin-B₁₂-Mangel) leiden, haben ein erhöhtes Risiko.

Aufmerksamkeit ist außerdem geboten, wenn trotz konsequenter medikamentöser Behandlung ein Magengeschwür nicht ausheilt und immer wiederkehrt.

Ein erhöhtes Krankheitsrisiko haben auch Menschen, die sich lange Zeit zuvor einer Magenoperation unterziehen mussten, beispielsweise aufgrund eines Magengeschwürs.

Rauchen

Auch das Rauchen gilt als Risikofaktor für Magenkrebs. Die zum Teil Krebs erregenden Stoffe des Zigaretten- und Tabakrauchs lösen sich im Speichel und gelangen so in den Magen. Man schätzt, dass Raucher ein etwa 3-fach erhöhtes Risiko haben, an Magenkrebs zu erkranken.

Genetische Veranlagung

Es gibt Familien, in denen gehäuft Magenkrebs auftritt. Nach Schätzungen der Wissenschaftler ist das persönliche Risiko, an Magenkrebs zu erkranken, etwa 3,7 mal größer, wenn ein Familienmitglied ersten Grades – d.h. Eltern, Kinder, Geschwister – bereits an einem Magenkarzinom erkrankt ist.

STADIENEINTEILUNGEN FÜR DAS MAGENKARZINOM

Das Magenkarzinom lässt sich in mehrere Klassifikationen einteilen, die jeweils klinische Bedeutung für die Therapieentscheidungen haben.

Stadieneinteilung

Diese Stadieneinteilung ist von großer Bedeutung zur Therapieplanung, da sie klinisch relevant ist. Tabelle 1 stellt die Einteilung mit Bezug der stadienbezogenen Überlebensraten dar (s.o.).

Histologische Klassifikation

- Papilläres Adenokarzinom
- Tubuläres Adenokarzinom
- Muzinöses Adenokarzinom
- Siegelringzellkarzinom
- Plattenepithelkarzinom
- Adenosquames Karzinom
- Kleinzelliges Karzinom
- Undifferenziertes (anaplastisches) Karzinom

Tab. 1: Stadieneinteilung (UICC/AJCC 1997) der Magenkarzinome und mittlere Überlebensraten

				5-Jahres-ÜL-Raten ¹
Stad. IA	T1	N0	M0	85,2 %
Stad. IB	T1	N1	M0	69,2 %
	T2	N0	M0	
Stad. II	T1	N2	M0	43,7 %
	T2	N1	M0	
	T3	N0	M0	
Stad. IIIA	T2	N2	M0	28,6 %
	T3	N1	M0	
	T4	N0	M0	
Stad. IIIB	T3	N2	M0	17,7 %
Stad. IV	T4	N1,2	M0	8,7 %
	jedes T	N3	M0	
	jedes T	jedes N	M1	

¹ Österreich. Ges. für Chirurgie

Der größte Anteil der Magenkarzinome sind Adenokarzinome.

Laurén Klassifikation nach dem Wachstumsmuster

Diese Klassifikation gibt Auskunft über das Wachstumsverhalten innerhalb der Magenwand. Dies ist wichtig zu wissen, da hieraus u.a. das Ausmaß der Operation bestimmt wird.

1. **INTESTINALER TYP:** Expansiv (polypös) wachsend und gut begrenzt
2. **DIFFUSER TYP:** Infiltrativ wachsend und schlecht begrenzt. Sonderform: Linitis Plastica mit Neigung zu frühzeitiger Lymphknotenmetastasierung
3. **MISCHTYP:** (Wird behandelt wie ein diffuser Typ)

TNM Klassifikation

Primärtumor (T)

- T1: Infiltration der Lamina propria oder Submucosa
- T2: Infiltration der Muscularis propria oder der Subserosa
- T3: Infiltration der Serosa (Viszerales Peritoneum) ohne benachbarte Strukturen zu infiltrieren.
- T4: Infiltration benachbarter Strukturen

Unsere Patienten kamen überwiegend in der Kategorie T2 oder T3 zur Therapie (Abb. 1).

Regionäre Lymphknoten (N)

- NX: Der Lymphknotenstatus kann nicht beurteilt werden
- N0: Keine regionären Lymphknoten vorhanden
- N1: Regionäre Lymphknotenmetastasen in 1–6 Lymphknoten

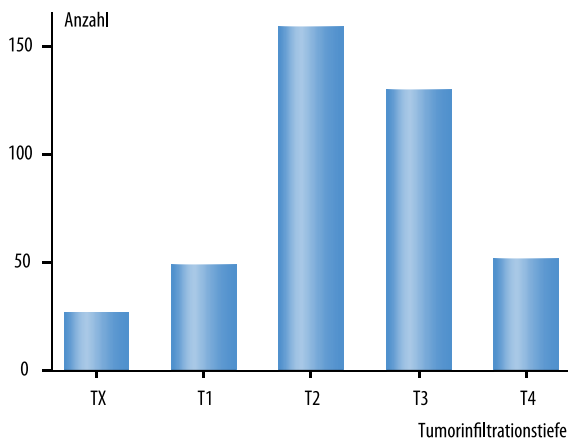


Abb. 1. Tumorstadien der Magenkarzinome in unserem Krankengut

- N2: Metastasen in 7–15 Lymphknoten
- N3: Metastasen in mehr als 15 Lymphknoten

Fernmetastasen (M)

- MX: Metastasenstatus kann nicht beurteilt werden
- M0: keine Fernmetastasen
- M1: Fernmetastasen

PROGNOSE DES MAGENKARZINOMS

Die Überlebensrate des Magenkarzinoms liegt in unserer Klinik bei ca. 40% (Abb. 2). Die allgemeinen durchschnittlichen stadienabhängigen Überlebensraten sind in Tabelle 1 dargestellt. Sie liegen beim Frühkarzinom bei über 85%, jedoch fallen sie im fortgeschrittenen Stadium auf unter 10% ab.

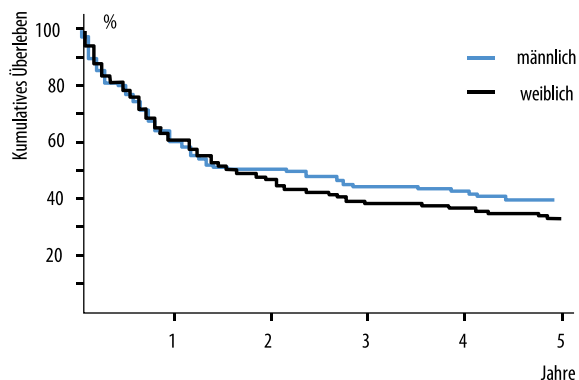


Abb. 2. Überlebensstatistik in unserer Klinik bei allen Tumorstadien

SYMPTOME

Das Magenkarzinom verursacht zu Beginn seines Wachstums keine oder nur sehr uncharakteristische Beschwerden. Diese werden oft gar nicht beachtet

oder als harmlose Nahrungsunverträglichkeiten fehlgedeutet. Tabelle 2 listet die aufgetretenen Symptome unserer Klinik auf, die die Patienten bei Diagnosestellung der Erkrankung aufgeführt haben. Aus diesem Grund ist es besonders wichtig, dass Sie die Risikofaktoren kennen und länger anhaltenden Magenbeschwerden unbedingt auf den Grund gehen. Treten bei Ihnen eine oder mehrere der im Folgenden genannten Beschwerden auf, sollten Sie auf jeden Fall einen Arzt aufsuchen, damit die Ursache rechtzeitig geklärt wird.

Tab. 2. Symptome mit Prozentzahlen bei Magenkarzinom in der Charité Campus Virchow Klinikum

Keine Beschwerden	45,4%
Sodbrennen oder Verdauungsstörungen	43,8%
Unbehagen oder Bauchschmerz	30,6%
Übelkeit und Erbrechen	41,7%
Diarrhö oder Obstipation	7,9%
Gebälär Oberbauch nach den Mahlzeiten	43,8%
Appetitverlust	43,8%
Schwäche und Müdigkeit	11,2%
Blutung (Bluterbrechen, Blut im Stuhl)	7,0%

DIAGNOSE

Tabelle 3 listet die erforderlichen Untersuchungen zur Sicherung und vor Behandlung des Magenkarzinoms auf. Bei Verdacht eines Magenkarzinoms muß die Diagnose durch Endoskopie und histologische Untersuchung gesichert werden. Anschließend müssen weitere Untersuchungen folgen, um das Ausmass der Erkrankung einzuschätzen. Weiterhin entscheiden die Untersuchungen über die Art der Therapie, die im Folgenden noch ausführlicher erläutert werden.

Tab. 3. Diagnostik beim Magenkarzinom

Körperliche Untersuchung
Endoskopie mit Biopsie
Endosonographie
Kontrastmitteldarstellung
evtl. CT Abdomen
evtl. Laparoskopie
evtl. Zytologie

Körperliche Untersuchung

Zunächst wird sich der Arzt ausführlich nach den Beschwerden und nach möglichen Risikofaktoren erkundigen und eine gründliche körperliche Untersu-

chung durchführen. Dadurch kann er schon wichtige Hinweise über die Art der Erkrankung gewinnen.

Magenspiegelung (Gastroskopie)

Die Magenspiegelung ist die wichtigste und aussagekräftigste Untersuchung zur Feststellung eines Tumors. Es werden Proben entnommen und zur Diagnosesicherung untersucht. Erst dann kann mit Sicherheit geklärt werden, ob Krebs vorliegt oder nicht.

Röntgenaufnahmen

Eine Röntgenuntersuchung des Magen-Darm-Traktes mit Kontrastmitteln kann in manchen Fällen – ergänzend zur Magenspiegelung – notwendig sein, um die Diagnose zu sichern. Mit Hilfe der Röntgenaufnahmen lässt sich bis zu einem gewissen Grad die Ausdehnung des Karzinoms sowie seine Auswirkung auf die Verdauung beurteilen. So sind beispielsweise Verengungen des Magens (Stenosen), die der Tumor verursacht, gut sichtbar.

Sonographie

Mit Hilfe des Ultraschalls kann der Arzt feststellen, ob der Tumor sich bereits auf andere Organe ausgebreitet hat (Metastasenbildung). Insbesondere die Leber, aber auch andere Bauchorgane, das Peritoneum sowie Lymphknoten werden auf Metastasen untersucht. Eine Endosonographie erlaubt eine genauere Aussage darüber, wie tief der Tumor in die Magenwand eingedrungen ist. Die Endosonographie ist die entscheidende Untersuchung zur Beurteilung der T-Kategorie und dient damit als Grundlage für die Entscheidung, ob der Patient eine neoadjuvante Therapie erhält oder primär operiert wird.

Computertomographie (CT)

Inzwischen ist diese Untersuchung Standard bei der Diagnostik. Fernmetastasen und das lokale Ausmass der Erkrankung können auf diese Weise zusammen mit den anderen Untersuchungen dargestellt werden.

Laparoskopie

Die Laparoskopie wird kontrovers diskutiert. Sie gehört nicht zum Standard in der Diagnostik, kann aber sinnvoll sein, um eine evtl. Peritonealkarzinose zu entdecken.

VERTEILUNG DER MAGENKARZINOME

Abbildung 3 zeigt die Verteilung der Tumoren auf die verschiedenen Magenabschnitte. In unserem Krankengut sahen wir eine gleichmäßige Verteilung in allen Abschnitten mit einem gewissen Vorsprung der

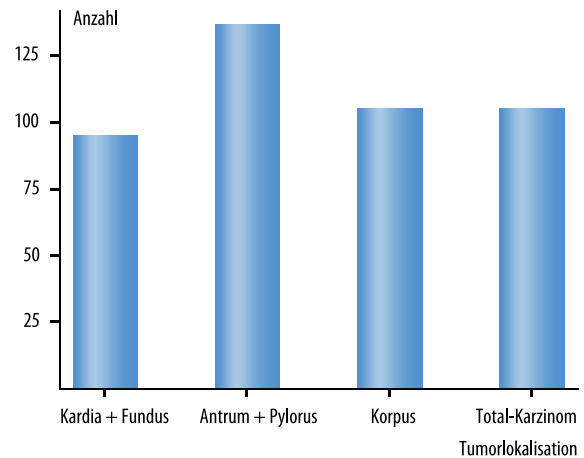


Abb. 3. Verteilung der Tumoren auf die verschiedenen Magenabschnitte in unserem Krankengut

distalen Karzinome. Die Verteilung der Karzinome bestimmt die Operationstechnik.

THERAPIE

Nachdem die Diagnose Magenkrebs gesichert ist und die Ausbreitung bestimmt worden ist, wird ein Therapiekonzept erstellt. Es werden folgende Therapiemöglichkeiten angewendet, die je nach Stadium alleine oder in Kombination untereinander durchgeführt werden.

- *die Operation*
- *die Chemotherapie*
- *die Strahlentherapie*

Nur durch eine Operation kann das Magenkarzinom geheilt werden. Als weitere Therapiemöglichkeiten stehen die Chemotherapie und in manchen Situationen auch die Strahlenbehandlung zur Verfügung. Neuere Untersuchungen zeigen, daß eine perioperative Chemotherapie mit einem neoadjuvanten und adjuvanten Teil z.B. nach dem MAGIC Schema die besten Ergebnisse aufweist und somit bei jedem Patienten ab Kategorie T3 in Erwägung gezogen wird. Es wurde ein Überlebensvorteil von 13% nach 5 Jahren in der Gruppe mit Chemotherapie und Operation gegenüber alleiniger Operation beobachtet. Es sollte immer eine stadiengerechte Therapie erfolgen, wie in Tabelle 4 aufgelistet ist. Während in den frühen Stadien die endoskopische Mukosektomie oder die primäre Operation erfolgt, werden die Patienten in höheren Tumorstadien kombiniert mit Chemotherapie und Operation behandelt.

DAS KARDIAKARZINOM

Besondere Aufmerksamkeit verdient das Kardiakarzinom, da es eine separate Einteilung besitzt und

Tab. 4. Stadiengerechte Therapie des Magenkarzinoms

Stad. IA	Endoskopische Lokale Tumorexzision
Stad. IB–IIIA	1. Perioperative Chemotherapie (MAGIC) mit ECF Schema (Epirubicin, Cisplatin und 5-FU) 2. Primäre Operation unter kurativem Ansatz
Stad. IIIB	1. Versuch des Downstaging durch neoadjuvante Chemotherapie nach dem MAGIC Schema mit anschließender Operation 2. Bei R1-Resektion evtl. postoperative Radiochemotherapie nach dem SWOG Protokoll (= 5-FU + Folinsäure → Bestrahlung + 5-FU + Folinsäure → 5-FU + Folinsäure)
Stad. IV	Palliative Behandlung. Dies wird individuell interdisziplinär entschieden 1. Palliative Resektion ohne Lymphadenektomie 2. Chemotherapie mit einem Schema der 3. Generation

differenziert behandelt wird. Nach den Kriterien der TNM Klassifikation wird das Kardiakarzinom den Magenkarzinomen zugerechnet. Es nimmt jedoch eine Stellung zwischen dem distalen Ösophaguskarzinom und dem Magenkarzinom ein. Es handelt sich um Adenokarzinome, welche im Bereich der Kardia entspringen und bei Diagnosestellung die Z-Linie mit erfaßt haben. Nach Siewert werden diese Tumoren in Typ I, II und III unterteilt (Abb. 4).

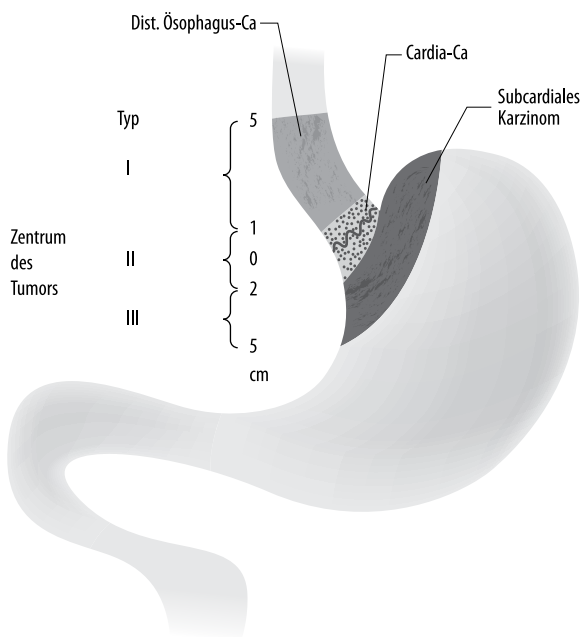


Abb. 4. Einteilung der Kardiakarzinome nach Siewert

- **Typ I:** Distaler Ösophagus: 1–5 cm oberhalb der Z-Linie, meist einer intestinalen Metaplasie eines Barrett Ösophagus entspringend

- **Typ II:** Eigentliche Kardiaregion: 1 cm oberhalb bis 2 cm unterhalb der Z-Linie, meist vom kardialen Epithel mit intestinaler Metaplasie ausgehend.
- **Typ III:** Subcardiale Lokalisation: 2 cm unterhalb bis 5 cm unterhalb der Z-Linie. Es infiltriert den gastroösophagealen Übergang und den distalen Ösophagus von unten.

Während seit den 30iger Jahren die distalen Magenkarzinome an Häufigkeit abgenommen haben, hat die Inzidenz von Kardiakarzinomen in den letzten 20 Jahren, insbesondere bei Patienten im Alter unter 40 Jahren, rapide zugenommen. Die Prognose der proximalen Karzinome liegt mit einer 5-Jahres Überlebensrate von 10–15% deutlich unter der der distalen lokalisierten Magenkarzinome mit 50%.

BEHANDLUNGSMETHODEN DES MAGENKARZINOMS

Die Operation

Der Kern der Behandlung ist die Operation, wenn eine Heilung angestrebt wird. Da eine Heilung nur durch die vollständige Entfernung des gesamten Tumorgewebes möglich ist, muss der Magen – je nach Lage und Ausdehnung des Tumors sowie der Gewebart des Tumors – ganz (Abb. 5) oder teilweise (Abb. 6) entfernt werden. In der Regel ist die Gastrektomie die Operation der Wahl beim Magenkarzinom, da ein Abstand des Tumors zum Resektionsrand beim intestinalen Typ bei 5cm und beim diffusen Typ bei 8cm bestehen muss. Somit können meist nur distale Magenkarzinome vom intestinalen Typ nach Lauren subtotal reseziert werden. Zur Gastrektomie gehört standardmäßig eine D2-Lymphadenektomie, die die komplette Entfernung aller Lymphknoten der Kompartimente I und II umfasst (Tab 5).

Erweiterte Gastrektomie

Bei fortgeschrittenen Tumoren mit Ausdehnung in angrenzende Organe wird die Gastrektomie erweitert.

1. ORALE ERWEITERUNG

Der untere Ösophagus wird insbesondere bei Kardiakarzinomen mitreseziert. Eine Schnellschnittuntersuchung des Schnitttrandes muß Tumorfreiheit aufzeigen. Die Höhe der Absetzungslinie wird durch die Lokalisation des Tumors bestimmt. In der Regel wird dies durch eine transhiatale Erweiterung erreicht, kann aber bei höherem Sitz einen Zweihöhleneingriff mit abdominothorakaler Ösophagusresektion erforderlich machen.

2. LINKS ERWEITERTE GASTREKTOMIE

Bei Tumorinfiltration in den Pankreasschwanz werden der Pankreasschwanz und die Milz mit rese-

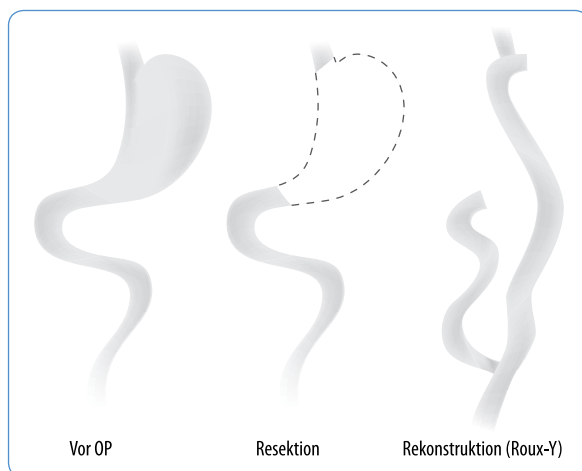


Abb. 5. Schematische Darstellung der Gastrektomie und der Rekonstruktion, wie sie an unserer Klinik durchgeführt wird

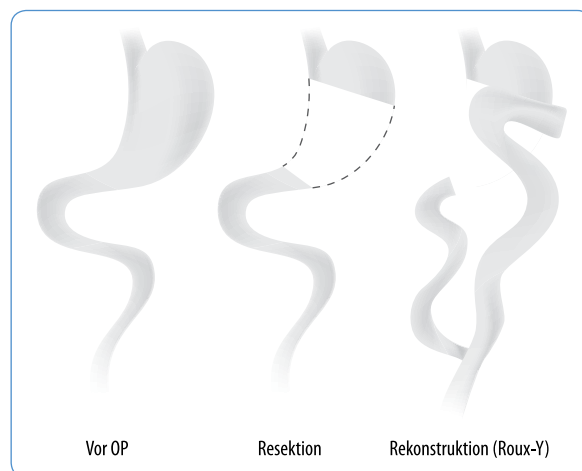


Abb. 6. Subtotale Gastrektomie mit Rekonstruktion durch Dünndarmschlinge nach Roux

Tab. 5. Lymphknotenkompartimente und -stationen

Kompartiment I	Kompartiment II	Kompartiment III
Perigastrische LK der Stationen 1-6	Lymphknotenstationen 7-11	Nicht regionäre Lymphknoten (Bei Befall = Fernmetastasierung)
1. Rechts parakardial 2. Links parakardial 3. Entlang der kleinen Kurvatur 4. Entlang der großen Kurvatur (4a: Aa Gastricae breves, 4b: A. Gastromentalis sinistra, 4c: A. gastromentalis dextra) 5. Suprapylorisch 6. Infrapylorisch	7. A. gastrica sinistra 8. A. hepatica communis 9. Truncus coeliacus 10. Milzhilus 11. A. lienalis	12. Lig. hepatoduodenale 13. Hinter Pankreaskopf retropankreatisch 14. Mesenterialwurzel 15. Colica media 16. Paraaortal 110. Paraösophageal 111. Zwerchfell

ziert. Die Resektion der linken Kolonflexur und der linken Nebenniere kann ebenfalls erforderlich werden. Abbildung 7 zeigt ein erweitertes Gastrektomiepräparat mit Splenektomie en bloc bei einem ausgedehnten intramural wachsenden Karzinom vom diffusen Typ

3. RECHTS ERWEITERTE GASTREKTOMIE

Beim Antrumkarzinom kann der Pankreaskopf infiltriert sein. In diesem Fall wird der Pankreaskopf im Sinne einer Whipple'schen Operation mit reseziert. Die Rekonstruktion erfolgt mit 2 nach Roux-Y ausgeschalteten Jejunumschlingen. Eine der Schlingen wird an das Pankreas und den Gallengang, die andere an den Ösophagus anastomosiert.

Als Magenersatz wird meist ein Segment des Jejunums verwendet (Abb 5). Die Rekonstruktion kann mit oder ohne Ersatzmagen erfolgen. Bei Vorliegen von Metastasen oder einer Peritonealkarzinose kann man zunächst versuchen, ihn durch eine Chemothe-

rapie zu verkleinern (neoadjuvante Chemotherapie). In manchen Fällen ist es anschließend möglich, das Geschwulst komplett zu entfernen. Haben sich bereits Metastasen in Leber, Peritoneum oder entfernteren Körperregionen gebildet, ist eine Heilung nicht mehr zu erzielen. Abb. 8 zeigt ein mit Metastasen im Sinne einer Peritonealkarzinose durchsetztes omentum majus. Eine Operation wird dann nur durchgeführt, wenn Komplikationen dies erfordern. Am häufigsten treten hier Blutungen und Stenosen auf, die eine Operation sinnvoll machen.

Operationstechniken des Kardiakarzinoms

Hier ist die Klassifikation nach Siewert zu berücksichtigen. Das Typ I Karzinom wird als distales Ösophaguskarzinom angesehen und wird somit mit einer thorakoabdominalen Ösophagusresektion operiert. Typ II und Typ III gelten als Magenkarzinome,

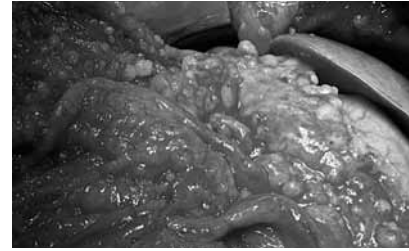
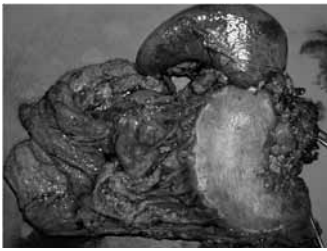


Abb. 7. Gastrektomie mit Splenektomie bei ausgedehntem Magenkarzinom. Die Magenwand ist mit Tumor durchsetzt

Abb. 8. Peritonealkarzinose mit Durchsetzung des omentum majus

die durch eine erweiterte oder reguläre Gastrektomie operiert werden.

- *TYP I* Abdominothorakale Ösophagusresektion mit Magenhochzug
- *TYP II* Erweiterte Gastrektomie
- *TYP III* Gastrektomie

Die Chemotherapie

Magenkarzinome werden heute allgemein als gut empfindlich für eine Chemotherapie angesehen. Eine Heilung des Magenkarzinoms allein durch die Gabe von Zytostatika ist allerdings nicht möglich. Die Chemotherapie hat einen wichtigen Platz in der Behandlung: So können bei einem lokal fortgeschrittenen Tumor durch eine Vorbehandlung mit Zytostatika etwa 50% der Patienten eine Verkleinerung der Geschwulst erreicht werden. Damit ist unter Umständen doch noch die vollständige operative Tumorentfernung möglich (neoadjuvante Therapie). Derzeit scheint eine Therapie mit 3 Zyklen ECF (Epirubicin, Cisplatin und 5-FU) den stärksten Effekt auf das Langzeitüberleben zu haben. Bei metastasierten Tumoren, ist die Chemotherapie palliativ.

Die Strahlentherapie

Die Strahlentherapie wird bei Magenkrebs gelegentlich eingesetzt, wenn ein Patient nicht operiert werden kann oder auf eine Chemotherapie nicht anspricht. Die Strahlentherapie dient vor allem der Behandlung der Schmerzen. Auch Metastasen können gelegentlich von einer Bestrahlung profitieren. Vor allem bei Knochenmetastasen, die Schmerzen, und unter Umständen auch Knochenbrüche, verursachen können, hat sich die Bestrahlung zur Linderung der Beschwerden bewährt. In jüngster Zeit wird die Strahlentherapie in Kombination mit einer Chemotherapie auch zusätzlich zur Operation durchgeführt. Bei lokal fortgeschrittenen Tumoren kann sie zusätzlich zur Chemotherapie zu einer Verkleinerung des Tumors beitragen und damit die vollständige Entfernung bei der Operation erleichtern (präoperative Chemo-

Radiotherapie). Sie scheint jedoch das Risiko für Komplikationen nach der Operation zu erhöhen. Deshalb ist nicht standardisiert. Nach einer kompletten Tumorentfernung soll die Chemo-Radiotherapie einen Rückfall der Tumorerkrankung verhindern. Dies ist jedoch bisher nur dann erwiesen, wenn die Operation nur eingeschränkt, d.h. ohne Entfernung der umgebenden Lymphknoten erfolgt ist. Die Wirksamkeit nach vollständiger Tumorentfernung ist hingegen nicht erwiesen.

ERNÄHRUNG UND FOLGEN NACH OPERATIONEN AM MAGEN

Die Physiologie des Magens

Der Magen nimmt die im Mund eingespeichelte, zerkleinerte und durch die Speiseröhre transportierte Nahrung auf und verarbeitet sie zu einem gut durchmischten Speisebrei weiter. Dazu produziert die Magenschleimhaut Salzsäure und eiweißspaltende Verdauungsenzyme, die die verschiedenen Nahrungsbestandteile zersetzen. Um sich selbst gegen die aggressive Magensäure zu schützen, wird die Magenschleimhaut von einem neutralen Sekret überzogen. Dort, wo diese Schutzschicht defekt ist, kann der Magen angedaut werden. Darüber hinaus wird im Magen der so genannte "Intrinsic Factor" gebildet, der für die Aufnahme von Vitamin B12 benötigt wird. Große Bedeutung für die gesamte Verdauung hat die Speicherfunktion des Magens. Bis zu acht Stunden kann die Nahrung hier lagern – das Fassungsvermögen beim Erwachsenen liegt bei 1,6 bis 2,4 Liter – bevor sie schließlich portionsweise an den Dünndarm weitergegeben wird. Eine teilweise oder völlige Entfernung des Magens führt zu vielfältigen Veränderungen des Verdauungsvorgangs. Das Spektrum reicht dabei von Appetitlosigkeit und Gewichtsabnahme bis hin zu Blutarmut und Osteoporose. Weitere Erscheinungen wie Sodbrennen, Durchfall, Druckgefühl im Oberbauch und Völlegefühl nach dem Essen können oftmals durch eine geeignete Diät, eine angepasste

Lebensweise sowie durch Medikamente behandelt werden können. Die Beschwerden werden von den Patienten sehr unterschiedlich empfunden. Einige Patienten sind trotz vollständiger Entfernung des Magens annähernd beschwerdefrei. Andere klagen über zum Teil erhebliche Beschwerden, selbst wenn ihnen noch ein Teil des Magens erhalten werden konnte.

Gewichtsverlust

Viele Magenoperierte klagen über Appetitlosigkeit. Eine wesentliche Ursache: nach der Operation ist die „Hungermeldefunktion“ des Magens, die durch Hormone gesteuert wird, gestört. Hinzu kommt, dass Magenoperierte die Nahrung schlechter verwerten können als gesunde Menschen und deshalb einen höheren Kalorienbedarf haben (etwa 20 bis 30% mehr). Eine Gewichtsabnahme in den ersten Monaten nach der Operation ist normal. Oft stabilisiert sich das Körpergewicht im Laufe des zweiten Halbjahres nach der Operation wieder – manche Patienten kämpfen aber auch längerfristig gegen Untergewicht.

Ernährungstipps bei „kleinem Magen“

1. Häufiger kleine Mahlzeiten zu sich nehmen, z.B. alle 2–3 Stunden.
2. Feste und flüssige Nahrung nicht gleichzeitig einnehmen. Nicht zu den Mahlzeiten, sondern schluckweise und in kleinen Mengen dazwischen trinken.
3. Sie zu heiße und zu kalte Speisen vermeiden.
4. Langsam essen und gut kauen, damit im Mund eine optimale Vorverdauung stattfinden kann.

Manchmal liegt die Ursache des Gewichtsverlustes aber auch in einer ungenügenden Verwertung des Nahrungsfettes. Neben den oben genannten Funktionen ist der Magen auch für das Zusammenspiel von Gallenblase, Dünndarm und Bauchspeicheldrüse unverzichtbar. Die Bauchspeicheldrüse produziert wichtige Enzyme für die Fettverdauung – eine Störung dieser Funktion hat eine Fettunverträglichkeit zur Folge. In der Regel können die Einnahme von Bauchspeicheldrüsenfermenten und die Aufnahme von bestimmten Fetten (MCT-Fette) hier Abhilfe verschaffen.

Das Dumping-Syndrom

Eine typische Begleiterscheinung einer Magen(teil)entfernung ist das so genannte „Dumping-Syndrom“. Der Ausdruck ist vom englischen Verb „to dump“ abgeleitet, das soviel wie „stürzen“ oder „hineinplumpsen“ bedeutet. Gemeint ist damit, dass der Speisebrei wegen der beeinträchtigten Speicherkfunktion des Magens zu schnell in den Dünndarm „stürzt“. Man unterscheidet dabei das Früh- und das

Spätsyndrom. Ersteres tritt innerhalb der ersten 15 Minuten nach Nahrungsaufnahme auf und äußert sich durch Druckgefühl im Oberbauch bzw. Oberbauchschmerzen, Übelkeit, Erbrechen, Schwäche- und Schwindelgefühl, Herzklopfen, Blässe, Schweißausbrüche und im Extremfall in einem Kreislaufkollaps. Weil der Speisebrei sturzartig im Dünndarm ankommt, wird dieser plötzlich und sehr stark überdehnt. Zusätzlich strömt Wasser aus der Blutbahn in den Darm, um den Speisebrei zu verdünnen, was die Dehnung des Darms noch verstärkt. Beides führt zu einem starken Abfall des Blutdrucks und damit zu den genannten Beschwerden.

Das Spätsyndrom äußert sich durch ähnliche Beschwerden, die aber erst ein bis vier Stunden nach dem Essen auftreten. Charakteristisch ist zusätzlich Heißhunger. Die Ursachen des Spätsyndroms sind jedoch andere. Aufgrund dessen der Speisebrei in einem Schwung im Dünndarm angelangt, wird der darin enthaltene Zucker sehr schnell vom Darm aufgenommen. Dadurch steigt der Blutzuckerspiegel – mit der Folge, dass Insulin ausgeschüttet wird, um den Blutzuckerspiegel wieder zu senken. Da kein Nahrungszucker mehr nachkommt, bleibt eine Unterzuckerung zurück, was zu Schweißausbrüchen, Konzentrationsstörungen und Müdigkeit führen kann. Die Beschwerden des Dumping-Syndroms lassen sich durch Ernährungsmaßnahmen meist gut abmildern. In den meisten Fällen bessern sie sich auch im Laufe der ersten Monate nach der Operation. Lassen Sie sich in jedem Fall von Ihrem Arzt beraten.

Sodbrennen und Erbrechen

Viele Patienten werden nach einer Magenoperation von Sodbrennen – gelegentlich auch Brechreiz – heimgesucht. In diesem Fall besteht die Gefahr einer Entzündung der Speiseröhre mit anschließender Vernarbung und Verengung. Diese Probleme können – je nach Sitz des Tumors und der Art der Operation – verschiedene Ursachen haben. In den meisten Fällen fließt die Magensäure in die Speiseröhre oder Magensaft und Speisebrei stauen sich im Restmagen. Wurde der gesamte Magen entfernt, dringen eventuell Dünndarmsäfte und Galle in die Speiseröhre vor, was zu den gleichen Beschwerden führen kann. Das Risiko, dass scharfe Verdauungssäfte ungehindert in die Speiseröhre eindringen können, ist dann am Höchsten, wenn bei der Operation der Schließmuskel zwischen Speiseröhre und Magen entfernt wurde.

Durchfall

Durchfälle nach einer Magenoperation können verschiedene Gründe haben. Zum einen können sie als Begleiterscheinungen des Dumping-Syndroms oder ei-

ner gestörten Fettverdauung auftreten. Dies kann auch der Fall sein, wenn bei der Operation die Vagusnerven durchtrennt wurden (Vagotomie).

Die Durchfälle können ferner dadurch bedingt sein, dass die Magensäureproduktion nach einer Operation eingeschränkt und die keimhemmende Funktion der Magensäure dadurch beeinträchtigt ist. Als Folge können vermehrt Infektionen auftreten, die von Durchfällen begleitet werden. In diesem Fall sollten Sie riskante Speisen wie rohes oder ungenügend gegartes Fleisch, rohe Eier und Rohmilchprodukte dringend meiden. Meist ist der Durchfall (gekoppelt mit Blähungen) die Folge einer Milchzuckerunverträglichkeit (Laktoseintoleranz), unter der 60% der Magenoperierten leiden. Ursächlich ist ein Mangel am Enzym Laktase, welches zur Verdauung von Milchzucker notwendig ist. Die Laktase wird zwar nicht im Magen, sondern im Dünndarm gebildet – doch wenn die Magenfunktion eingeschränkt ist oder fehlt und der Dünndarm deshalb stark mit Speisebrei belastet wird, stellt sich bei Magenoperierten häufig ein Laktosemangel ein. Die einhergehenden Beschwerden lassen sich mit einer angepassten Ernährungsweise vollständig beheben.

Vitamin B₁₂-Mangel

In der Magenschleimhaut wird der so genannte „Intrinsic Factor“ gebildet, der notwendig ist, um im Darm Vitamin B₁₂ aus der Nahrung aufzunehmen. Vitamin B₁₂ spielt eine entscheidende Rolle bei der Blutbildung im Knochenmark und hilft beim Aufbau des gesamten Nervensystems. Zwar kann das Vitamin in der Leber gespeichert werden – aber spätestens nach einigen Jahren tritt bei Patienten, deren Magen vollständig entfernt wurde, ein Vitamin B₁₂-Mangel auf, der unbehandelt schwerwiegende Folgen zeitigen kann. Die typische Mangelkrankheit ist die perniziöse Anämie. Bei dieser Form der Blutarmut sind die roten Blutkörperchen vergrößert und unreif, sodass sie ihrer Aufgabe, Sauerstoff im Blut zu transportieren, nicht mehr richtig nachkommen können. Dies äußert sich zunächst durch Müdigkeit und Schwächegefühle, später durch eine vermehrte Blutungsneigung und möglicherweise Störungen des Nervensystems. Es ist unbedingt erforderlich, dass Vitamin B₁₂ nach einer Magenentfernung regelmäßig gespritzt wird. Eine Zuführung in Tablettenform wirkt nicht, da die Mangelercheinung eben nicht auf einen Engpass beim Vitamin selbst, sondern beim „Intrinsic Factor“ zurückzuführen ist, der nach der Operation nicht mehr oder nicht mehr ausreichend gebildet wird.

Osteoporose

Des Weiteren sind Magenoperierte aus zwei Gründen einem erhöhten Osteoporose-Risiko ausge-

setzt. Erstens kann die beeinträchtigte Fettverdauung zu einer mangelhaften Aufnahme des fettlöslichen Vitamins D und – infolgedessen – zu einem Kalziummangel führen. Wenn der Patient darüber hinaus keinen Milchzucker verträgt und aus diesem Grund die Aufnahme von Milch und Milchprodukten einstellen muss, steht noch weniger Kalzium zur Verfügung, weil die Gewährleistung einer ausreichenden Kalziumversorgung ohne Milch und Milchprodukte beinahe unmöglich ist. Wenn Sie ein paar Ernährungstipps befolgen, können Sie auch hier gut vorbeugen.

THE EVALUATION OF COAL MINERS' BLOOD CELLS RESISTANCE UNDER THE DUST AEROSOLS INFLUENCE

L.K. Ibrayeva MD, I.A. Amanzhol MD

The national center for occupational hygiene and occupational diseases, Karaganda, Kazakhstan

Under present-day conditions, while new economic relations are developing and forms of property are modifying, the health preservation of workers in essential industries became more difficult. The health analysis of people, who working under the harmful industrial conditions, argues the maintaining of a high level of occupational diseases in leading industries. The socio-economic compensation for their health damages requires large expenditures.

Generally, the existing methods of dispensary and clinical examination are focused on the diagnosis of nosological pathologic forms and don't allow to recognize and differentiate prenosological states. The examination of "almost healthy people" shows that the highest incidence of the adaptive mechanisms' stress and their disruption accounts for workers aged 20–40 years.

THE PURPOSE

is the stability rating of coal miners' blood cells under the dust aerosols influence.

MATERIALS AND RESEARCH METHODS

As a result of our experimental research there were devised diagnostic approaches, which characterize the tolerance of organism to the dust aerosols effects. There were revealed that the main effect under the influence of different types of fine dust aerosols is a violation of the cell membranes integrity, which leads to the development of pathological states of experimental animals in different body systems. A erythrocytes stability determination to haemolysis is the main method, which available to detect the presence of the membrane damaging effect under various xenobiotics influence. In our experiments there were revealed that under different kinds of fine dust dust aerosols influence already since the early timing the erythrocytes stability to haemolysis has been decreased, which indicates the presence of the membrane damaging effect.

There were tested 290 people. 270 of them are almost healthy workers from the Karaganda mine



Lyazat K. Ibrayeva
Associate Professor,
Head of the Department
of Management of Scientific
Research, Head of Toxicology
Laboratory
lyazat1967@gmail.com

named after Kostenko with different work experience (113 drifters and 157 breakage face miners), working under the most adverse conditions (dust 90–150 mg/m³), and 20 healthy donors who do not have and had no contact with the dust during their careers. The examined people age was within 20–50 years old. Every examined person didn't have a history of chronic diseases. The selection of the miners was conducted during a medical examination in the medical unit "Ispat-Karmet." The control group includes 20 donors. Drifts and breakage face miners were divided into groups based on the length of their work experience with 5 years step.

Every selected individual (miners and donors) was determined full blood count (hemoglobin, hematocrit, red blood cell count and white blood cells) by the usual method [1] with the hematology analyzer System KX-21N (Japan, 2006), erythrocytes stability to haemolysis, which indicates a violation of the cell membranes stability by Jager FC [2] SF-2000 with the CF-2000 spectrophotometer (Russia, 2006).

The statistical analysis of the material was hold with a PC Pentium IV using the «Statistika 5.0» application package. There were performed the calculation of the reliability coefficient (P), which was estimated from the Student value, table test (t) of the ANOVA, correlation analysis, regression analysis, factor analysis [3–6].

RESULTS OF OWN RESEARCHES

The drifters who have been working in the dust under 20 years of the hemoglobin level was above the control level by 10–11%, and who have been worked over 20 years – above 12%. The number of red blood cells in all the drifters experienced groups was 6–8%

lower than in the control group. The hematocrit of drifters who have been working in the underground dust under 10 years was not significantly different from the control group, and at the experience of 11–20 years it became 23% higher than in the control group, indicating the blood clots development. At the same time drifters in 11–15 years experienced group have hematocrit of 20% more than in 6–10 years experienced group, and in 20 years experienced group it have grown by 8% compared to 11–15 years experienced group. The level of hemolyzed erythrocytes of the drifters who have been working up to 20 years was higher than control in 3 times, and have worked over 20 years – in 2 times. At the same time in comparison with previous groups there weren't observed any significant changes in drifters erythrocyte haemolysis (Table 1).

face miners' haemolysis level of red blood cells was higher in 2 times than it in the 20 years experienced group, and 76% more than it in the more 20 years experienced group. Comparing the level of red blood cells haemolysis with a previous experienced group of breakage face miners, as well as between similar groups of stope miners and drifters there were found no significant differences (Table 1).

Using a pair of correlation analysis it is confirmed that with increasing doses of received dust, that is length of career, the degree of red blood cells hemolysis increases ($r = 0,153$), which indicates the presence of dust effect which damages membranes. The drifters in major had leukopenia ($r = -0,430$), haemolysis of red blood cells ($r = 0,356$) and blood clots ($r = 0,408$).

Table 1. The blood picture of breakage face miners and drifters by experienced groups

Groups	Leukocytes, * 10-9 / l	Hemoglobin, g / l	Erythrocytes * 12.10 / L	Hematocrit, ml	Haemolysis,%
Control	7,20±0,148	140,5±1,16	5,35±0,130	0,40±0,006	1,280±0,072
Drifts	5,17±0,167*	155,2±2,60*	4,97±0,088*	0,41±0,007	4,352±1,619
	5,11±0,094*	155,9±1,38*	5,01±0,035*	0,41±0,009	4,088±1,099*
	5,12±0,076*	156,6±1,12*	4,97±0,041*	0,49±0,008*#	3,369±0,747*
	5,26±0,053*	155,1±1,93*	4,92±0,056*	0,49±0,006*	4,195±0,838*
	4,95±0,059*#	156,9±0,63*	4,98±0,026*	0,53±0,009*#	2,855±0,559*
Breakage face miners	4,85±0,119*	153,3±0,73*	4,77±0,037*	0,41±0,012	2,660±0,535*
	4,95±0,065*	154,8±0,95*	4,93±0,035*#	0,41±0,006	2,626±0,595*
	5,15±0,077*	156,7±1,27*	5,00±0,044*	0,44±0,011*#^	2,927±0,477*
	5,20±0,065*	157,4±0,66*	5,00±0,026*	0,48±0,007*#	2,735±0,490*
	5,09±0,070*	157,5±0,51*	4,97±0,048*	0,48±0,005*^	2,256±0,283*

Note: The accuracy compared with the control – *; with the previous experienced group – #, with a similar drifters group – ^.

The hemoglobin level of stope miners with the experience under 10 years was higher than controls at 9–10%, and with the experience 11 years or more it became by 12% of control values. The number of erythrocytes was reduced on 11% relative to control in stope miners, who have been working less than 5 years, and who have been working 6 years and more has been below 8.7% in controls. The level of hematocrit at the stope miners 10 years experience was not significantly different with the control, and with a length of 11–15 years it was 10% more than in the control.

At the same time stope miners with 11–15 years experience have hematocrit level which is 10% lower than a similar group of drifters. In 11–15 years experienced group the hematocrit became 17% more than in 6–10 years experienced group, and with the 16–20 years career – 9% more, than at the 11–15 years experience. In addition, breakage face miners with more 20 years experience had level of hematocrit which was 9% lower than in the same group of drifters. All breakage

Thus, even with a 5 years career as drifters', as stope miners' hemoglobin levels increased and the number of white blood cells reduced. However, the drifters with the more than 20 years experience have progressed leukocytes reducing by 6% compared with 16–20 years experience. In the 11–15 years experienced group there was a hematocrit increasing by 23% for drifters and by 10% for breakage face miners. In the sequel with increasing the length of the dust experience in both cases there was a hematocrit increasing by 8–9% compared with the previous experienced group, with the difference that for drifters it occurred before the 16 years dust experience, while for stope miners it occurred only after the 20 years dust experience. In less 5 years experienced group the stability of red blood cells to haemolysis have decreased in 3 times for drifters and 2 times for breakage face miners. The findings suggest a more pronounced degree of blood clots, a leukopenia and a decreasing the stability of erythrocytes to haemolysis for drifters.

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THE ESTIMATION OF EFFICIENCY OF THERAPY AT SICK OF THE CHRONIC DUST BRONCHITIS AT THE STATIONARY STAGE OF MEDICAL REHABILITATION

G.T. Igimbaeva, S.S. Kojgeldinova, A.U. Amanbekova, B.A. Abdigozhina, G. N. Azhimetova

The national center of factory hygiene and occupational diseases, Karaganda, Kazakhstan

THE URGENCY

Preservation and strengthening of a manpower of Republic Kazakhstan is the basic condition for creation of steady financial and economic and resource base of the state, the further economic development of the country and growth of its total national product.

Medical rehabilitation – necessary, and quite often obligatory stage of treatment of patients with the various diseases, directed on restoration of the broken functions, work capacity of the patient, improvement of quality of life and the social status.

The existing approach to medical rehabilitation of patients with occupational diseases including a dust etiology, it is based on preventive maintenance principles, taking into account influence of the basic damaging factors and the most suffered bodies and systems of an organism with algorithms of rehabilitation [1, 2].

Treatment and rehabilitation are closely connected among themselves, mutually supplement each other and shouldn't be in confrontation. It is erroneous to perceive rehabilitation as an aftercare of the patient since rehabilitation methods are applied, since the earliest stages of disease. Regenerative treatment as the basis of medical rehabilitation, is a method of pathogenetic therapy [3].

Use in system of treatment-and-prophylactic actions at patients with diseases of easy bronchial spasmolytics and expectorant means, certainly, remains in the classical way of traditional treatment, meanwhile, for the purpose of optimization of spent medical rehabilitation, important complex application both traditional, and new means of medicamentous and non-drug treatment.

PURPOSE

To Develop programs of medical rehabilitation at workers of group of "risk" of development of a dust pathology and patients with occupational diseases of lungs.

MATERIALS AND RESEARCH METHODS

On the basis of clinic NTS GT and PZ MZ RK 43 patients, from them are surveyed: – 1 group (CDBII, n=15) – sick of a chronic dust bronchitis with respiratory insufficiency of II degree, receiving basic therapy; – 2 group (CDBII, n=28) – sick of a chronic dust bronchitis with respiratory insufficiency of II degree, receiving basic therapy in a combination to a treatment-and-prophylactic complex;

Course of treatment has made 10 days. Prior to the beginning of treatment at patients the written informed consent to carrying out of treatment-and-prophylactic actions undertook.

The information on distribution of participants on intervention groups remained as fiduciary till the moment of appointment of treatment. Registration and distribution of participants on groups was carried out by the responsible person from among research assistants of laboratory of a dust pathology. To the clinical personnel and the researchers, not engaged for registration and distribution of participants on groups, the accessory of patients to this or that group wasn't known. At all stages of a spent course of treatment-and-prophylactic actions the initial quantity of the surveyed remained. Criterion of preservation of quality of measurements was performance of functional researches by highly skilled experts in functional diagnostics.

Basic therapy includes:

– **NON-DRUG TREATMENT:** 1) a mode III; 2) a table № 15; 3) medical gymnastics, course of treatment – 10 employment, rate slow, amplitude incomplete, loading minimum; 4) independent employment in chamber 2 times a day – respiratory exercises;

– **MEDICAMENTOUS TREATMENT:** 1) mucolitic therapy: Ambroscolum 30 mg on 1 t x 3 times a day within 14 days (strengthens physiological activity vibrating epithelium and peristaltic movements bronchiols, promoting advancement of a phlegm from

the bottom departments in the top departments of respiratory ways and to its deducing); 2) Tocopherolum acetate of 200 mg 2 times a day within 14 days (protect various substances from oxidizing changes);

Medical – the preventive complex «Wobenzym+ Vitrum+Phytotea +Aeroionization» included:

- Wobenzym under the scheme: on 3 tablets 3 times a day, 30 minutes prior to meal, washing down with a water glass (200 ml);
- Vitrum Beauty Elite under the scheme: on 1 tablet 2 times a day;
- Phytotea under the scheme: on 1 bag 3 times a day;
- Aeroionization was spent with aeroionizer “NPA-0001” RK-MT-5 N00155 use under the following scheme: 1st session of 5 minutes at concentration of negative aeroions of oxygen (AI) to 10 thousand in 1 cm³ of air. In the subsequent sessions were extended on 5 times with maintenance AI to 100, 300, 400, 500, 600, 700, 800, 900 thousand and 1 million in 1 cm³ of air accordingly.

On each surveyed the card of clinical inspection including was filled: a passport part, a professional route, the anthropometrical data, data on bad habits, the subjective and objective data. The estimation of efficiency of treatment-and-prophylactic actions was spent by double registration of indicators of the general analysis of blood, the FLOOR-AOZ (TBK-JET products, dyen conjugates, double communications, tryens, a catalase in blood plasma), functions of external breath, blood gases, bodyplethyzmography before course of treatment.

Function of external breath was investigated on the automated spirometric analyzer of breath “the HELL-02M” (manufacture – Kazan). Following indicators were defined: vital capacity of lungs (VCL), the forced vital capacity of lungs (FVCL), volume of the forced exhalation for 1 second (FE1), an index of Tiffno (FE1/ FVCL), peak volume speed (C), the maximum volume speeds at level of 25,50,75% (MVS25, MVS 50, MVS 75). The received sizes of measured indicators compared to their due sizes in percentage terms.

Gases arterial blood were defined on a computer gas analyzer “Stat profile 5” (“Nova biomedical”, the USA). Registered following parameters: a negative logarithm of ions of hydrogen (pH), partial pressure of oxygen (pO₂), saturation oxygen (O₂sat), partial pressure of carbonic gas (pCO₂), true bicarbonate (AB), standard bicarbonate (SB), the sum of all buffer bases (BB), surplus or deficiency of the bases (BE).

Cardiopulmonary diagnostic system PADS (Patient Diagnostic System), by Medset, Germany (bodyplethyzmography) and hardware-software er-

gospurometric module: program Ergo Spirometry for PADS, the appendix to diagnostic system PADS.

The volume of the spent researches is presented in table 1.

Object of biochemical researches was blood plasma. The blood taken from an elbow vein, was separated in a centrifuge at 3000 rpm within 10 minutes for branch of plasma from weights of the red cells.

In blood plasma defined indicators the POL – dyen conjugates, tryens and double communications, TBK-reactivity products in blood plasma [4, 5].

The statistical analysis of results of research spent with program use «STATISTICA» – version 6.0 on the computer «Athlon 2500XP +», text editor Microsoft Word 2003.

Digital values of investigated indicators are statistically processed with calculation of arithmetic average, its errors (m). For definition of reliability of distinctions between average values of compared parameters used criterion of Student. Significance values – 0,05 were taken into consideration; 0,01; 0,001. For the purpose of definition of degree of communication between two random variables carried out the correlation analysis, counted correlation factor (r) [6, 7].

RESULTS AND DISCUSSION

At research of indicators the POL-AOZ before treatment in 1 to group sick of a chronic dust bronchitis with respiratory insufficiency of II degree, receiving basic therapy, is marked authentic decrease tryens and double communications on 33% and 36% accordingly, the tendency to decrease in level of TBA-reactivity products and dyen conjugates on 2% and 7% accordingly, and activity of a catalase remains without changes. In 2 group sick the chronic dust bronchitis with respiratory insufficiency of II degree, receiving basic therapy in a combination to a treatment-and-prophylactic complex, reveals authentic decrease in level of TBA-reactivity products, tryens, dyen conjugates and double communications on 14%, 48%, 49% and 33% accordingly, and activity of a catalase has authentically raised in 1,6 times (table 2).

So, at comparison of the received data in both groups decrease in activity of pathological products the POL in group of the patients receiving against basic therapy medical-preventive a complex that speaks positive action of components of the last on a process condition free radical oxidations of lipids that leads to regulation of process of the oxidizing metabolism providing stability of cytoplasmatic membranes to oxidizing stress by decrease of pathological activity of lipoperoxidation against strengthening of system of antioxidant protection in the form of authentic increase of activity of a catalase several times is observed.

Table 1. Objects and the methods of research spent at sick chronic dust bronchitis with respiratory insufficiency II degree

The work maintenance	Quantity of the surveyed	Quantity of the investigation
Clinical investigations:	43	348
Definition dyen conjugates, tryens and double communications in blood plasma (m.u.)	43	258
Definition TBA-reactivity products in the plazma of the blood (mkmol/ml)	43	86
Analyses of the function of external breath's function	43	860
Definition Gas structure of blood	43	258
Bodyplethyzmography	43	258
Total:	43	2068

Table 2. Indicators the POL-AOZ in plasma of blood at sick of a chronic dust bronchitis with respiratory insufficiency of II degree before and after therapy ($M \pm m$)

Indicators	I group (CDBII + BT, n=15)		II group (CDBII+BT + TPC, n=28)	
	before BT	after BT	before TPC	after TPC
TBA-ПП, mkmol/ml	3,01±0,19	2,94±0,25	1,33±0,31	1,14±0,26*
Tryens, m.u./ml	0,18±0,06	0,12±0,009*	0,25±0,06	0,12±0,04*
DC, m.u./ml	0,15±0,01	0,14±0,02	0,15±0,05	0,077±0,033*
Double communications, m.u./ml	0,047±0,007	0,03±0,006*	0,09±0,03	0,03±0,01*
Каталаза, mkkat/ml	13,51±2,48	13,7±1,99	5,44±0,9	8,74±0,08*

Note: * – Reliability of distinctions with control ($p < 0,05$) BT – basic therapy, TPC – treatment-prevention complex

Table 3. Indicators OAK at sick of a chronic dust bronchitis with respiratory insufficiency of II degree before and after therapy ($M \pm m$)

Indicators	I group (CDBII + BT, n=15)		II group (CDBII+BT + TPC, n=28)	
	before BT	after BT	before TPC	after TPC
Hb	144±3,85	141,93±3,35	144,96±2,22	166,78±1,9
red (blood) cells	4,60±0,01	4,73±0,01	4,78±0,01	4,76±0,06
leucocyte	6,16±0,37	5,4±0,029*	9,59±0,025	6,28±0,03*
bazophyles	1,0±0,06	1,06±0,06	0,78±0,01	0,46±0,09*
eozinophyles	3,26±0,04	2,5±0,027*	1,89±0,028	1,57±0,02*
stabs	2,6±0,03	2,26±0,024	0,78±0,012	0,46±0,09*
segmentated cell	61,2±0,16	62,866±0,05	61,14±0,012	62,75±0,20
lymphocytes	28,53±0,016	32,00±0,09*	33,28±0,016	32,57±0,13
monocytes	4,00±0,052	4,26±0,056	4,57±0,039	3,78±0,027*
thrombocytes	207,13±6,24	207,73±6,91	228,85±1,78	226±6,25

Note: * – Reliability of distinctions with control ($p < 0,05$), BT – basic therapy, TPC – treatment-prevention complex

Efficiency of the spent therapy it was observed and at research of the general analysis of blood before therapy. In I group the tendency to decrease in level of hemoglobin on 2%, a tendency to increase in level of leukocytes on 3% is revealed. From leukocytes, eozynophyles and lymphocytes authentic decrease on 12%, 23%, 12% accordingly is marked. Other indicators of the general analysis of blood without special changes. In II group of patients authentic decrease in quantity of leukocytes, basophiles, eozynophyles, stabs and monocytes on 34%, 41%, 17%, 41% and 17% accordingly is revealed, thus hemoglobin level has authentically raised on 15% (table 3).

The analysis at research of indicators of function of external breath before therapy has shown that in IY to group surveyed against the spent medical actions authentic increase VCL, FVCL, FE_1 , $FE_1/FVCL$, MVS25, MVS50, MVS75 and V2/V1 on 7%, 11%, 17%, 8%, 16%, 17% and 12% accordingly is observed. In YI to group of the surveyed authentic increase VCL, FVCL, FE_1 , $FE_1/FVCL$, MVS25, MVS50 and MVS75 on 19%, 15%, 15%, 8%, 24% and 29% accordingly (table 4) is revealed.

From table 5 it is visible that in I group at research of indicators bodyplethysmography authentic increase total amount of lungs (TAL) is revealed

and residual capacity of lungs (RCL) on 21% and 16% accordingly, the tendency to parity decrease between TAL and RCL to 3% at the same time is observed, and in II group the indicators TAL set forth above and RCL have increased by 38% and 11% accordingly, and the parity has changed towards reduction by 31% that testifies to more expressed efficiency of therapy in group of the patients receiving basic therapy in a combination to a treatment-and-prophylactic complex.

Thus, the revealed changes from volume of the forced exhalation, an index of Tiffno, RCL, being «the gold standard» for diagnostics of diseases of lungs and important spirographyc indicators of the obstructive syndrome, more expressed at use of in addition treatment-and-prophylactic complex, specify on regression of the bronchoobstructiv syndrome and a syndrome of respiratory insufficiency which are shown and in improvement earlier us of the described subjective and objective symptoms.

The positive effect from the spent actions was observed and in dynamics of changes of indicators of gas structure of arterial blood. In I to group the tendency to indicator increase pO_2 on 6% is revealed. Level O_2 sat, pCO_2 practically remains without changes. In II to group after the combined application of basic therapy and a treatment-and-prophylactic complex the authentic increase pO_2 and O_2 sat on 16% and 21% accordingly is observed, thus level partial pressure of carbonic gas authentically decreases on 48% (table 6).

Hence, medical rehabilitation at the persons, consisting in group of the patients with chronic dust bronchitis, should include along with the traditional actions, including expectorant therapy (Brongexinum, Ambrobene, Ambroxolum), directed on improvement of drainage function of lungs; bronchial spasmolytics (Teophyllinum, Teotardum), directed on restoration of bronchial passableness and activation mucociliaris epythelium; antioxidants (tocopherol acetate), directed on decrease in activity of lipoperoxidation's process; physiotherapy (a magnetotherapy, Ultra-violet irradiation); TFE (respiratory gymnastics, phytobolgygymnastic), system enzymotherapy (Wobenzym, rendering anti-inflammatory, and immunomodulated effect), a polyvitaminic and polymineral complex (Vitrum Beauty Elite participating in basic metabolic processes, improves microcirculation); the aereoionization providing anti-inflammatory effect.

Table 4. Indicators of function of external breath at sick of a chronic dust bronchitis with respiratory insufficiency of II degree before and after therapy ($M \pm m$)

Indicators	I group (CDBII + BT, n=15)		II group (CDBII+BT + TPC, n=28)	
	before BT	after BT	before TPC	after TPC
VCL	61,00±0,38	65,33±0,31*	71,75±0,23	85,62±0,77*
FVC	54,33±0,31	60,53±0,30*	73,32±0,37	84,35±0,74*
FE ₁	44,33±0,29	51,93±0,27*	61,8±0,24	70,97±0,61*
FE ₁ /FVCL	74,40±0,40	80,46±0,47*	77,07±0,32	83,26±0,73*
MVS 25	36,00±0,36	41,93±0,38*	46,88±0,27	58,17±0,37*
MVS 50	29,06±0,31	33,86±0,27*	39,62±0,40	51,00±0,28*
MVS 75	27,26±0,31	30,46±0,21*	37,74±0,38	39,30±0,27
V2/V1	2,74±0,15	2,22±1,21*	3,12±0,12	2,57±0,06

Note: * – Reliability of distinctions with control ($p < 0,05$), BT – basic therapy, TPC – treatment-prevention complex

Table 5. Indicators of the bodyplethizmography at sick of a chronic dust bronchitis with respiratory insufficiency of II degree before and after therapy ($M \pm m$)

Indicators	I group (CDBII + BT, n=15)		II group (CDBII+BT + TPC, n=28)	
	before BT	after BT	before TPC	after TPC
TAL, ml	96,6±0,5	117,2±9,7	100,7±0,03	138,43±0,043
RCL, ml	99,4±3,6	115,2±2,5	90,1±0,46	100,12±0,012
TAL/RCL, %	32,5±0,5	31,6±0,5	32,79±0,79	22,67±0,057

Note: * – Reliability of distinctions with control ($p < 0,05$), BT – basic therapy, TPC – treatment-prevention complex

Table 6. Indicators of gas structure of blood at sick of a chronic dust bronchitis with respiratory insufficiency of II degree before and after treatment ($M \pm m$)

Indicators	I group (CDBII + BT, n=15)		II group (CDBII+BT + TPC, n=28)	
	before BT	after BT	before TPC	after TPC
pO_2 , mm. Hg.	47,68±2,88	50,56±3,10	61,74±1,65	71,55±1,27
pCO_2 , mm. Hg.	39,31±0,70	38,96±0,76	37,98±0,79	18,17±1,15
O_2 sat, %	83,98±1,86	83,28±2,07	79,92±3,23	96,50±2,8

Note: * – Reliability of distinctions with control ($p < 0,05$), BT – basic therapy, TPC – treatment-prevention complex

OPTIMAL TARGET HEMOGLOBIN LEVEL IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND ANEMIA TREATED WITH ERYTHROPOIESIS-STIMULATING AGENTS: CONTROVERSIAL ISSUES

**L.V. Kozlovskaya MD, Yu.S. Milovanov MD,
L.Yu. Milovanova MD**

*I.M. Sechenov First Moscow State Medical University,
Moscow, Russia*

Anemia is a classical complication associated with chronic kidney disease (CKD). Frequency and intensity of anemia grows along with renal impairment progression [1–4]. In a number of recent studies with various populations of CKD patients the connection between anemia and increased risk of death, cardiovascular complications (CVC) and CKD progression has been established [3–6]. So in the recent cohort retrospective USA study with 5 885 CKD and estimated level of hemoglobin (Hb) patients, the degree of unfavorable anemia effects on the fatal outcomes from any reason, frequency of hospitalizations due to cardiovascular complications and due to end-stage kidney disease (individually for each end point) has been analyzed by method of cox-regression model [7]. In comparison to the patients without anemia, a higher death rate (hazards ratio – 5,27; 95% confidence interval – 4,37–6,35), a higher frequency of hospitalizations due to cardiovascular complications (hazards ratio – 2,18; confidence interval – 1,76–2,70) and of CKD end-stage cases (hazards ratio 5,46; confidence interval 3,38–8,82) have been registered among the patients with the most severe anemia, moreover, hazards ratio reflected changes in hemoglobin level and glomerular filtration rate. Association of anemia with the studied end points became more close along with anemia getting more severe. On the basis of the research results it was concluded that hemoglobin reduction is not just a marker of CKD progressive but also is independent and direct predictor of unfavorable prognosis and complications associated with CKD.

However, despite on the obvious relevance of the renal anemia correction problem its decision raises a number of questions. First of all concerns of the optimal target hemoglobin level in the each clinical setting. And, to a lesser extent, it concerns of the individual erythropoiesis-stimulating agents (ESA)



*Lidia V. Kozlovskaya
MD, Professor, Department
of Therapy and Professional
Diseases*



*Yury S. Milovanov
MD, Associate Professor,
Department of Nephrology and
Hemodialysis,
yumil2010@rambler.ru*

Abstract

Controversies in strategy of achievement and maintenance of target hemoglobin level in conditions of chronic kidney disease and approaches to optimization of erythropoiesis-stimulating agents use are discussed in the article.

Keywords

chronic kidney disease, anemia, target hemoglobin level

efficiency which used to reach the optimal target level because of almost all used today ESAs can effectively increase hemoglobin concentration in patients with CKD and anemia.

The ambiguous results of the recent cohort and scale retrospective studies of ESAs' effect in the patients with CKD of dialysis and pre-dialysis stages have become the subject of the unceasing discussion carried on in the medical press about target hemoglobin level. Analysis of these results has allowed tracing the history of the problem development and coming to certain conclusions.

The earlier studies [8–11] proved the positive effect of hemoglobin level normalization and erythropoietin therapy on general and cardiovascular survival

of the patients undergoing renal replacement therapy (RRT). The results of multicenter study meta-analysis of the program hemodialysis patients conducted in 5 European countries allowed getting the data which confirm the link of the high hemoglobin level with reduction of the relative death risk and/or hospitalization [11]. Hemoglobin level normalization in this period seemed to be an indispensable condition of anemia treatment for both hemodialysis and pre-dialysis CKD patients. But as experience of anemia treatment with epoetin drugs was accumulated, this initial view was questioned as a subset of patients with CKD when the seemingly optimal level of hemoglobin there is a tendency to raise blood pressure, measured by an increased need for antihypertensive drugs or marked change in the rheological properties of blood with development of thrombosis [12–17]. Thus, an optimal target hemoglobin level in patients with renal anemia both in dialysis and pre-dialysis stages remained undefined.

G.F. Strippoli with co-authors [18] performed a systematic analysis of 15 randomized controlled studies. The consequences of maintaining “low” ($Hb \leq 11$ g/dl, $Ht \leq 33\%$) or “high” ($Hb \geq 14$ g/dl, $Ht \geq 40\%$) hemoglobin level in pre-dialysis CKD and undergoing RRT patients were considered. A. Besarab with co-authors [16] in the largest open prospective study evaluated the risks and benefits of maintaining the normal level of hematokrit (Ht) among the hemodialysis patients with heart diseases. 1233 hemodialysis patients with associated chronic cardiac insufficiency or coronary heart disease (stenocardia, catheterization of coronary vessels or myocardial infarction) were involved in the study. (The patients with IV functional class (according to NYHA classification) chronic cardiac insufficiency were excluded as well as those having severe hypertension with diastolic blood pressure equal to or over 100 mm Hg). All the participants had the basis Ht level from 27 to 33% and had been taking a fixed moderate dose of epoetin alfa during the preceding 4 months. 618 (group 1) out of all the patients were randomized to normal Ht level (42%) for the achievement and maintained of which required increasing of the initial epoetin dose of 3 times. 615 (group 2) patients remained at the basis low Ht level (30%). After 29 months (observation period varied from 4 days to 30 months, the median of 14 months) the risk of reaching the primary endpoint (death or non-fatal cardiac infarction) was 7% higher among the patients with high (normal) Ht level, than among the patients from the control group (183 death cases and 19 non-fatal cardiac infarctions vs 150 death cases and 14 non-fatal cardiac infarctions; hazards ratio 1,3, 95% confidence interval 0,9-1,9). Causes of death

in 2 groups were similar, in most patients these were cardiovascular complications (sudden cardiac arrest, fatal acute myocardial infarction, arrhythmia, cerebrovascular events, etc.). Thrombosis of vascular access occurred more often in the group of patients with high Ht level (39% vs 29%, $p = 0,001$). At the same time, the quality of life evaluated by the scale of physical activity was higher among the patients with normal Ht level ($p=0,03$). But this advantage of the high Ht level was considered as less significant in comparison to the cardiovascular complication risk. The study was completed ahead of schedule (previously planned 3 years). Taking into account all the rest 14 studies, the results of which were processed with methods of G.F. Strippoli's meta-analysis authors made a conclusion that if hemoglobin level is maintained equal to or under 11 g/dl, risk of death among the patients with CKD and cardiovascular pathology is considerably lower than among the patients with hemoglobin level close to 14 g/dl. It should be noted that G.F. Strippoli with co-authors [18] analyzed a mixed groups of patients with CKD as the presence and absence of severe cardiovascular disease

In the study of H. Furland, T. Linde, J. Ahlmen and others [19] which included 416 pre-dialysis CKD and dialysis patients without severe concomitant cardiovascular pathology and/or coronary heart disease there were no difference in general mortality rate and rate of death due to cardiovascular complications between the group in which hemoglobin level was maintained in “normal” level (11–12 g/dl) and the group in which the hemoglobin level was maintained in “optimized” level (13,5–16 g/dl) in the course of the study period (12–19 months). At the same time no indisputable data confirming advantages of the policy of maintaining an increased hemoglobin level in comparison to a lower level (11–12 g/dl) were obtained.

Furland with co-authors' [19] study results pointed out that Strippoli with co-authors' [18] conclusions are not applicable to patients without cardiovascular pathology. In the randomized controlled study which was conducted by J. Rossert and co-authors [20] and published afterwards, authors compared two groups of patients – one with high hemoglobin level (13,0–15,0 g/dl) and another with lower one (11,0–12,0 g/dl), and thus evaluated effects of anemia correction by subcutaneous use of epoetin alfa on CKD progression. Decrease of glomerular filtration rate (GFR) was slower (though not statistically significant) in the group of patients with high (normal) hemoglobin level than in the group of patients with low hemoglobin level (0,058 versus 0,08 ml/min/1,73 m²/month). Despite the short duration of the trial (on average, 7,4 and 8,3 months respectively) on the basis of these data

it was concluded that normalization of hemoglobin level in CKD patients as a whole is safe, improves life quality and may slow the decline in GFR. At the same time the frequency of cardiovascular complications in patients with normal (high) level of Hb was no less than in the patients with low levels of it (25% and 18%).

On the basis of these studies, in May 2006 a working group of NKF-KDOQI (National Kidney Foundation – Kidney Disease Improving Outcome Quality Initiative) published clinical practical guidelines for anemia treatment in conditions of CKD. According to these guidelines, target hemoglobin level for patients with CKD treated with ESA in general should be $\geq 11,0$ g/dl (lower limit) but there is no ground to maintain it at the level over 13,0 g/dl (upper limit) [21]. By that time (end of 2006) the results of two large randomized studies [14, 15] had been published. Within the limits of these studies, effects of full anemia correction on general and cardiovascular mortality among the pre-dialysis CKD patients were published. The studies results had a significant impact upon further problem development. In CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with epoetin beta) study included 603 patients from Europe, Mexico and Asia predominantly with the IV stage of CKD accompanied with anemia, no advantage of normal target hemoglobin level (13,0–15,0 g/dl) versus the subnormal one (10,5–11,5 g/dl) was detected. In the course of the 3 year study the two groups did not differ much in the number of cardiovascular complications (158 vs 147), no differences either in general death rate or in hospitalization rate were registered. Both groups had almost the same mean value of GFR decrease within the 3 year period (3,4 vs 3,1 ml/min). However, the number of patients who reached hemodialysis within this period was more among those which had high hemoglobin level [14].

CHOIR study (Correction of Hemoglobin and Outcomes in Renal Insufficiency) involved 1432 patients with III and IV CKD stage, was interrupted ahead of schedule (before the planned 16 months) because of the risk of reaching the primary composite endpoint (death, myocardial infarction, hospitalization due to chronic cardiac insufficiency) turned out to be higher by 34% ($p < 0,03$) in the group of patients randomized to the hemoglobin level 13,5 g/dl than among the patients with the level 11,3 g/dl [15]. The CHOIR study patients population was characterized with a large number of diabetes mellitus patients, elderly patients suffering of arterial hypertension being a reason of kidney affection.

The mean dose of epoetin alfa used in this study was considerably higher (almost 3 times) than in

the CREATE and other studies. The fact that the majority of the patients in the treated group, despite on high doses of epoetin, did not reach the target hemoglobin level of 13,5 g/dl, was explained with high co-morbidity, although not ruled out the role of the epoetin vasoactive properties, its ability to stimulate of norepinephrine-L-1 (3,4 dioxypheyl-2 aminoethanol) and provoke of hypertension independently of the hemoglobin level changes [22]. Among the anemia-evoking factors in conditions of diabetes mellitus, chronic inflammation and pro-inflammatory cytokines (interleukin-1, tumor necrosis factor-alfa, interferon-gamma) are taken into consideration. Their heightened level in serum is detected before renal insufficiency development [54].

These 2 studies, though very different in the kind of participants and the results of the secondary analyses, have shown that full correction of anemia don't reduce death rate or cardiovascular complications rate in patients with CKD compared with partial correction of anemia. They have as well shown that high ESA doses can be ineffective (not able to increase hemoglobin level up to the target one) and even dangerous for the patients with comorbid conditions. Obviously, different populations of patients need individual recommendations regarding the treatment [23]. Moreover it is still not completely clear of ESA therapy to affect whether inhibition of CKD progression.

The results of meta-analysis conducted by Phrommintikul A. and co-authors [24] included also CREATE and CHOIR, have confirmed the thesis that CKD patients with accompanied of high target hemoglobin level have significantly higher risk of death from various reasons and arteriovenous access thrombosis.

NKF-KDOQI working group has introduced changes into its recommendations of 2006 regarding target level of hemoglobin in patients with CKD on the basis of the new data. To substantiate the new revision of the recommendations, the group has carried out an extended meta-analysis of all results by that time completed randomized controlled studies in the area of anemia treatment. Unlike Phrommintikul A. and his co-authors [24], NKF-KDOQI working group considered separately dialysis and pre-dialysis patients. The analysis has shown that among the pre-dialysis CKD patients, there was no significant difference in general mortality rate (8 studies – 3038 intent-to-treat patients) between the group with a higher hemoglobin level and group with a lower one, while cardiovascular complications risk (6 studies – 2850 intent-to-treat patients) was higher among the patients randomized to a higher target hemoglobin level (hazards ratio 1,21; 95% confidence interval 1,02–1,5). Among the

dialysis patients there was no significant difference in general mortality rate (4 studies – 2391 intent-to-treat patients) or cardiovascular complications rate (3 studies – 1975 intent-to-treat patients) between the group with a higher hemoglobin level and group with a lower one. According to the revised recommendations of NKF-KDOQI working group (September, 2007), target hemoglobin level should make up 11-12 g/dl and not exceed 13,0 g/dl for the patients undergoing ESA therapy, “since the possibility of harm from high- hemoglobin level exceeds the potential benefit of improving the quality of life and reducing the blood transfusion” [21].

Coordination meeting convened in October, 2007, within of KDIGO (Kidney Disease Improving Global Outcome) to elaborate a common position with respect to NKF-KDOQI publication of 2007, recognized that taking into consideration the latest data contained in the above mentioned publication, hemoglobin level exceeding 13,0 g/dl can be unsafe for the people used ESA therapy and that hemoglobin level ranging from 9,5 to 11,5 g/dl is associated with better outcomes than the level over 13,0 g/dl. Nevertheless, it was agreed that the new data are insufficient to justify an immediate revision of the recommendations for treatment of patients with CKD and anemia.

ERBP working group for anemia research (European Renal Best Practice) considered sufficient grounds to support the NKF-KDOQI recommendations 2007 to keep relatively low target hemoglobin level as a more secure hemoglobin level. At the same time, according to the group, the probability of harm from achieving a high target hemoglobin level while there, but it is mainly in certain populations of patients - those with diabetes mellitus, clinically significant cardiovascular diseases. [51].

Secondary CHOIR analysis was involved a large amount of such patients has shown that among the patients whose hemoglobin level did not reach the target one of 13,5 g/dl but who had a higher hemoglobin level in comparison to the control group, unfavorable outcomes like death or thrombosis were more often. Besides, the patients who needed high-dose ESA, marked by a 6% greater risk of end point studies, regardless of the hemoglobin level [21].

ERBP group underlined the importance of understanding whether the adverse events related to treatment with ESA only attempt to achieve higher hemoglobin level in patients with comorbidity, or they are caused by a reduced response of the patients for treatment of ESA. TREAT (The Trial to Reduce Cardiovascular Events with darbepoetin alfa) study which was finished in November, 2009, played an important role in support of the ERBP group opinion about

target hemoglobin level [47]. Within this multicenter placebo-controlled study, cardiovascular outcomes (death, non-fatal myocardial infarction, cardiac insufficiency, stroke or hospitalization due to myocardial ischemia) and renal outcomes (terminal stage of kidney disease and death) were evaluated in the 4038 patients with type II diabetes associated with pre-dialysis CKD and anemia (12 of patients were kept under observation in our clinic). Two groups of the patients were compared: a group randomized to full correction of anemia with darbepoetin alfa (target hemoglobin level – 13,0 g/dl) and placebo group (with “saving” 9,0 g/dl hemoglobin level). At the end of the observation period (on average 29,1 months) the patients in the first group reached the primary cardiovascular composite endpoint as often as the patients in the second group (hazards ratio 1,05; 95% confidence interval 0,94–1,17, $p=0,41$); there was no difference between the two groups in the frequency of another primary end point, i.e. death or terminal stage of renal disease (hazards ratio 1,06; 95% confidence interval, $p=0,29$), either. But analysis of certain elements of the end points revealed an increased risk of fatal and non-fatal cerebral stroke among the patients who had in their anamnesis a carried stroke, which were treated with darbepoetin alfa and were randomized to the target hemoglobin level equal to 13,0 g/dl (101 cases vs 53 in the placebo group, hazards ratio 1,92; $p<0,001$). In this group a higher frequency of death from malignant tumors (if there were tumors in the anamnesis), from venous and arterial thromboembolism was registered. However, heart revascularization operation in the darbepoetin group was needed less often than in the placebo group. Full anemia correction provided only moderately more favorable effect on the patients' life quality in comparison to the placebo group patients. But it should note that half of the patients of control group were treated with intravenous injections of iron and hemotransfusions while their hemoglobin level was observed. Thus, it is questionable if this group satisfies the criteria for placebo group.

The secondary analysis of TREAT results [26] confirmed the necessity to be cautious when correcting anemia in patients with diabetes and CKD. On the other hand, it should not ignore the fact that mean dose of darbepoetin alfa used in this study was around 175 mcg/month, that is 2 times more than a mean ESA dose given to hemodialysis patients in Europe. It follows that complications hazard could be to a greater extent more caused by high ESA dose than by hemoglobin concentration that was discussed while the secondary analysis of CHOIR study [26]. It is difficult to give an unambiguous interpretation of TREAT results because new secondary CHOIR analysis [27] on a het-

erogeneous model did not confirm that the risk grows due to a higher target hemoglobin level in patients with diabetes and those with cardiac insufficiency.

The results of secondary analyses of CHOIR studies, US Normal Hematocrit trial [28] showed as well that the patients who had the worst outcomes had been resistant to the treatment and so had been given higher doses of ESAs. According to ERBP group's opinion [25], ESA dose necessary for reaching target hemoglobin level (11,0–12,0 g/dl without intentional increase up to 13,0 g/dl) should be taken into consideration for evaluation of possible complications during treatment. Thus, if there is no need in ESAs or only small ESA doses are needed for maintaining target hemoglobin level, there are much fewer reasons to fear of adverse events, first, increased thrombotic effects, than in cases when high ESA doses are needed to reach this hemoglobin level. At the same time, unexpected data obtained in TREAT study: more frequent of deaths from malignant tumors (in case there was a tumor in the anamnesis) was among the patients randomized to darbepoetin alfa and full anemia correction (1,9% from 2 012 patients in the treatment group and 1,2% from 2 026 patients in placebo group, $p=0,08$). These data, despite small sampling, is in accordance with the results of meta-analysis of randomized studies in the oncology area which give evidence of increase in tumor growth and death rate among the patients with certain types of cancer due to ESA use [52]. ESA can promote growth of tumors through increased angiogenesis in cancer tissue after connection of exogenous erythropoietin to erythropoietin receptors expressing on cancer cells surface. Besides, use of ESA in patients with cancer can increase the risk of venous thromboembolism [21, 57, 58].

It is notably difficult to keep patients' hemoglobin level within a narrow range of target hemoglobin concentration values.

The effect of short-acting epoetin use in 281 patients being given hemodialysis treatment was subject to retrospective analysis: in the course of one year approximately three cycles were noted, which were characterized by increasing of the mean hemoglobin level up to 12,8 g/dl and its decrease to 10,3 g/dl, in most cases (84% episodes) due to the change of epoetin dose which was made on average 6 times a year [53].

Use of iron preparations, extension of intervals between introductions of erythropoiesis stimulators with a short elimination also contributed to the cyclic fluctuations in hemoglobin level. According to the our data and literature sources, patients with chronic cardiac insufficiency, systemic diseases and undercurrent infections are subject to significant fluctuations in hemoglobin level [29–34].

In a large observational study from the USA [29] (152 846 hemodialysis patients treated with ESA) found that many patients reach the target hemoglobin level, but not its stability (Fig. 1): only 10,3% of the patients had a stable hemoglobin level over a period of 6 months, while target hemoglobin level maintained itself in the course of that period only in 6,5% of the patients. The rest of the patients had fluctuating hemoglobin level over that period; in 40% cases it crossed both minimal and maximal limits of the target hemoglobin level range.

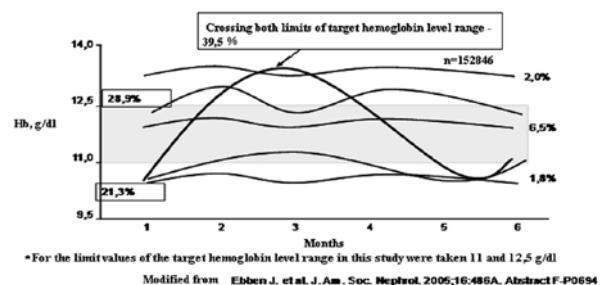


Fig.1. In 40% patients hemoglobin concentration value in the course of 6 month therapy crosses both minimal and maximal limits of the target hemoglobin level range

In this study the relation between hemoglobin concentration variability and unfavorable outcomes over 6 month period was evaluated [29]. The groups of patients were formed on the basis of mean monthly hemoglobin level (low level Hb < 11 g/dl; intermediate level Hb = 11,0–12,5 g/dl; high level Hb ≥ 12,5 g/dl) and on the basis of hemoglobin concentration fluctuations (constant value, low- and high-amplitude fluctuations). The groups were compared by morbidity and hospitalization rate.

Association between hemoglobin concentration variability and frequency of unfavorable outcomes was found. Among all considered groups, the patients with constantly low hemoglobin level had highest risk of morbidity and hospitalizations.

In another study conducted in the USA [30] (159 720 hemodialysis patients treated with ESA), the same algorithm was used: mean monthly hemoglobin concentration (low, intermediate, high) and the most considerable fluctuations of hemoglobin concentration over 6 month period (low-lower, low-high) were measured. The task of the study was to evaluate relation between hemoglobin parameters and death rate. It was established that the determining factor in death risk evaluation is general direction of hemoglobin level deviations from target values. Death risk growth was

associated with stably low hemoglobin level or with hemoglobin reduction over a period of time (under 11 g/dl in the course of over 3 months) and high variability of hemoglobin level. The lowest death rate was among the patients with CKD with stable hemoglobin level within the range from 11 to 12,5 g/dl.

Lately, a European study which included 5037 hemodialysis patients has been published [50]: in a multifactor model it was found that stably low hemoglobin level is an independent death rate predictor. There was established the importance of risk factors and other hemoglobin level changes such as, for example, high-amplitude fluctuations of hemoglobin level and stably high hemoglobin level, however, in adjusted model they did not prove it.

A more lengthy reduction of hemoglobin concentration down to under 11 g/dl before start of epoetin use as well as a more lengthy period of reaching target hemoglobin level (11–12 g/dl) make the risk of hospitalization and fatal outcome go up [35–37]. This fact should be taken into consideration when one chooses ESA prescription scheme.

Despite certain inconsistency, the results of these studies in total allow to make a conclusion that an important task when treating anemia in patients with CKD is to reduce fluctuations (variability) of target hemoglobin level within optimal range towards minimal as well as maximal limit.

One of the approaches to this problem solution can be use of long-acting epoetins, such as darbepoetin alfa and mircera for renal anemia treatment [37, 39–40].

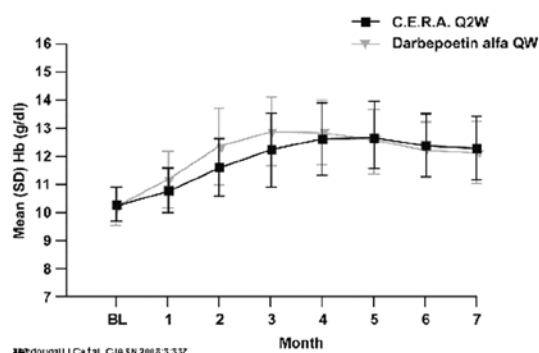
Darbepoetin alfa molecule contains 2 more N-combined carbohydrate chains which impart to it a higher metabolic activity in vitro; darbepoetin alfa molecule's final half-life period is three times longer than that of epoetin alfa, this property allows using of darbepoetin alfa once in 1–2 weeks to the patients undergoing RRT well as to the pre-dialysis CKD patients.

Even more lengthy period of action has III generation drug with brand name Mircera (methoxy polyethylene glycol - epoetin beta) – a long-acting erythropoietin receptors activator, which differs from epoetin beta by having in its molecular structure a long polymer chain (polyethylene glycol) [57]. Molecular weight of Mircera (two times heavier than epoetin beta) determines the pharmacokinetic and receptor interaction characteristics of this drug. Mircera is the only drug which, being once a month provides stable and constant control of hemoglobin level independently of the previous other erythropoiesis stimulators scheme use.

The results of the open randomized darbepoetin alfa and Mircera studies confirmed their safety and

efficiency for subcutaneous and intravenous introduction once of 1–2 weeks and once of 2–4 weeks respectively [34]. In ARCTOS study [37], which included 324 patients with pre-dialysis CKD, efficiency of subcutaneous Mircera (C.E.R.A.) and darbepoetin alfa was compared: 162 patients used Mircera (once in 2 weeks) and 162 patients used darbepoetin alfa (once a week) in the course of 18 weeks of the correction period and 10 weeks of the maintenance therapy. Increase of hemoglobin level was registered in 97,5% of the patients used Mircera and in 96,3% of the patients used darbepoetin alfa. Hemoglobin level remained stable in both groups over the whole study period, and the patients tolerated the therapy well (Fig. 2).

Mean Hb values during the correction and evaluation periods with C.E.R.A. and darbepoetin alfa (ITT population).



Source: American Society of Nephrology

CIASN

Fig. 2. Results of ARCTOS study (Clin. J. Am. Soc. Nephrol. 2008; 3(2): 337–347)

The ability of long-acting erythropoietin to restore and maintain stable hemoglobin levels in patients with various stages of CKD in combination with a decrease in the multiplicity of drug administration provides predictable control of hemoglobin level and simplifies the treatment of anemia for doctors and patients.

For economic calculations (Saueressing U., 2007) [51], the cost of anemia treatment by short-acting drugs (injections 3 times per week) in the dialysis Center in Germany amounted to an average of 17000€/100 patients, in Great Britain – 18379£/100 patients (excluding the cost of epoetin). In case of replacement of short-acting stimulant epoetin on long-acting erythropoiesis – Mircera (1 injection once a month) the cost of anemia treatment in the dialysis Center in Germany could be reduced by 58%, in Great Britain – 35%.

Currently, two drugs approved for clinical use and are available in our country.

In 2009 ERBP working group has summarized the results of the controlled studies of the recent years (TREAT, CHOIR, CREATE, US Normal Hematocrit Trial) and formulated its position with respect to anemia treatment and target hemoglobin level in patients with CKD [25]. The following conclusion can be made on the basis of these recommendations.

It is getting more and more evidents that the common "protocol" approach to renal anemia treatment does not provide improvement of ESA therapy results. Anemia management in patients with CKD requires individual approach taking into account the influence of the underlying disease of CKD, comorbidities, environmental factors and some other reasons individual for each patient. Choice of target hemoglobin level makes up an important part of therapy strategy.

ESA therapy of anemia should be started when 2 consecutive blood tests made with two-week interval have shown that hemoglobin level is under 11 g/dl (for patients of high risk, such as, for example, with II type diabetes mellitus and with cardiovascular complications in the anamnesis – when hemoglobin level is under 10 g/dl), but only in case no other reasons for anemia except CKD were detected within the diagnostic tests.

The newly obtained data allow recommending a narrow range of target hemoglobin concentration values: 11–12 g/dl and the values not exceeding 13 g/dl for the majority of patients with CKD and anemia.

For patients with CKD combined with a severe pathology (such as diabetes mellitus and cardiovascular complications) it would be justified to establish target hemoglobin level within the range of 10–12 g/dl (but not over 12 g/dl, especially for those who have risk of stroke). On the other hand, for patients with CKD without any combined severe pathology, it is common to establish target hemoglobin level within the range of 11–12 g/dl. This range can be accidentally exceeded due to hemoglobin variability, but not over 13 g/dl.

Patients with CKD who have in their anamnesis oncological diseases should be prescribed the possible lowest ESA doses, on the basis of careful analysis of "damage-benefit" relation. For patients with nonhematologic tumors (solid tumors) and anemia which treated with chemotherapy, ESA therapy is justified for the purpose of reducing frequency of hemotransfusions. In this case target hemoglobin level should not exceed 12 g/dl, keeping within the range between 9,0 and 11,0 g/dl. One should be very careful with hemotransfusions: if possible, hemotransfusions should be avoided before renal transplantation [25, 57, 58].

At the beginning of ESA therapy patients with CKD and anemia should be given low ESA doses, af-

ter some time ESA dose should be titrated in order to prevent quick increase in hemoglobin concentration. At the first stage of the therapy hemoglobin concentration should increase at a rate of 1–2 g/dl/month, hemoglobin concentration increase by more than 2 g/dl per month is undesirable. If dose escalation does not lead to hemoglobin concentration increase, before doing further correction one should carefully evaluate the risk for the given patient and determine the most acceptable ESA dose for this patient, as well as exclude the possibility of interrelation between anemia severity degree and extrarenal causes.

Varying hemoglobin levels is expected, but the large fluctuations, as well as constantly low or constantly high values beyond the target level should strive to avoid.

In each particular case certain factors which are related to the therapy or to the patient should take into consideration in order to minimize ESA dose and to maintain stable hemoglobin level within the target range.

All CKD patients with anemia, which is planned to epoetin therapy, require the prior correction of iron deficiency, preferably by intravenous iron administration. Adequate intake of iron is an important element of supportive ESA treatment.

For the dialysis patients, important conditions of inflammation risk reduction and improvement of response to ESA therapy are as follows: high quality of dialysis water and biocompatibility of membranes, everyday dialysis and operative hemofiltration, hyperparathyroidism correction, malnutrition correction.

One should take into account impact of drugs, in particular of angiotensin-converting enzyme inhibitors, because angiotensin II takes part in erythropoiesis regulation and its inhibition leads to weakening of response to erythropoietin, thus, being in certain cases a reason for erythropoietin resistance [55].

Pharmacological characteristics of the various ESA, including frequency of administration, dose required to achieve the target level of hemoglobin may determine the choice of ESA. For not on dialysis patients subcutaneous administration and less frequent dosing regimen, ie, use of long-acting ESA is more convenient, at the same time for patients receiving regular dialysis treatment, these parameters can not be preferred.

Benefits and risks of ESA therapy should be straightforwardly discussed with the patient as well as the purposes of therapy which can be different depending on the patient's way of life – active or passive.

In current medical literature is put up for discussion the question: do we need new studies on the ESA treatment and the target hemoglobin level in CKD patients? It appears clearly needed to better understand

the relationship between the hemoglobin concentration, the dose of ESA and the features of the underlying kidney disease.

Anemia is a modifiable risk factor and its correction on the safe level not only improves life quality of patients, but can also decelerate CKD progression, that is why renal anemia treatment remains one of the most relevant issues in nephrology.

For sure, the treatment of anemia in patients with CKD will be improving and becoming more individual by way of taking into consideration underlying kidney disease and comorbidity, as well as the factors influencing erythropoiesis in each patient (iron metabolism, infections and inflammation, dialysis parameters, protein-energy status, intake of drugs, etc.).

Individual approach to the selection of optimal target hemoglobin level will allow to go beyond of a narrow hemoglobin corridor of 11,0–12,0 g / dL is recommended for patients with CKD in general, to reduce its variability, and thus to optimize the strategy for the treatment of anemia in predialysis as well as in dialysis CKD patients.

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THE PLACE OF PARICALCITOL IN NEPHROPROTECTIVE STRATEGY OF PREDIALYSIS CHRONIC KIDNEY DISEASE DUE TO SYSTEMIC DISEASES

**L.Yu. Milovanova MD, Yu.S. Milovanov MD,
L.V. Kozlovskaya MD Prof.**

*I.M. Sechenov First Moscow State Medical University,
Moscow, Russia*



Liudmila Yu. Milovanova
Department of Nephrology
and Hemodialysis, MD, Research Fellow
lussyja2000@mail.ru

Abstract

Nephroprotective strategy for the predialysis stages of chronic kidney disease (CKD) is aimed the maximum reduction of proteinuria (microalbuminuria) and the simultaneous normalization of hypertension as the most weighty of glomerulosclerosis progression factors. Among the lowering proteinuria means the early systematic calcitriol use in combination with renin-angiotensin system (RAS) blockers, erythropoietin and lipid-lowering drugs plays an especially important role.

The aim of the study

was a comparative analysis of calcitriol and paricalcitol effects to proteinuria reduce and secondary hyperparathyroidism (SHPT) development prevention in patients with systemic diseases and III–IV CKD stage.

Patients and methods

The study included 50 patients with CKD stage III–IV due to systemic diseases (35 systemic lupus erythematosus and 15 different forms of systemic vasculitis), which were divided into 2 groups. The 1 st group consisted of 28 patients (8 to III and 20 IV stage, which was used calcitriol at a dose of 0.25 mcg/day. In group 2 included 22 patients (9 with III and 13 with IV stage), they were administered paricalcitol 1 mg per day.

Calcitriol and paricalcitol with nephroprotective aim applied when the level of the blood intact parathyroid hormone (iPTH) was not below 65 pg/ml, and based on indicators of phosphor-calcium exchange. The 1 st and 2 nd groups' patients were required to appoint RAS blockers, erythropoietin with iron preparations, and statins. In 11 patients of group 1 and 12 patients in group 2 at admission and at the end of the study period Doppler ultrasound of common carotid arteries was performed.

Results

Prior to calcitriol and paricalcitol treatment, proteinuria was $1,3 \pm 0,5$ g/day in group 1 and $1,2 \pm 0,3$ g/day in group 2, and the level of PTH, respectively, – 76 ± 18 , 6 pg/ml and $82 \pm 16,6$ g/ml. Combined calcification/atherosclerosis lesion of common carotid arteries was detected in 27,3% patients in group 1 and 33,3% in group 2. Calcitriol and paricalcitol were tolerated satisfactorily.

As a result, after 3 months from the beginning of these drugs use in patients with initially diagnosed increased PTH levels in the blood was reached the normalization of its content.

Reducing proteinuria occurred more rapidly ($p < 0,05$), while reducing hypertension by the end of 3 months was more significant ($p < 0,01$) in patients received paricalcitol, than with calcitriol.

During the same period among 12 patients in group 2 at 4 with diagnosed arteriosclerosis/calcification, episodes the hypercalcemia, as well as the progression of atherosclerosis/calcification were not identified. In contrast, among patients treated with calcitriol episodes of hypercalcemia were recorded at 27,3%, while in 3 patients with diagnosed during the screening arteriosclerosis/calcification were observed its progression

Conclusion

Application of paricalcitol at the predialysis stage of CKD due to systemic disease with hyperparathyroidism accompanied not only normal levels of PTH, but also a significant decrease in daily proteinuria and hypertension.

Keywords

chronic kidney disease, hemodialysis, secondary hyperparathyroidism, parathyroid hormone, proteinuria, paricalcitol.

BACKGROUND

Nephroprotective strategy for the predialysis stages of chronic kidney disease (CKD) is aimed the maximum reduction of proteinuria (microalbuminuria) and the normalization of hypertension as the most

weighty factors of glomerulosclerosis progression. Early systematic use of calcitriol in combination with blockers of the renin-angiotensin system (RAS), an erythropoietin drugs and lipid-lowering drugs among the lowering proteinuria means plays an especially important role.

The final aim is to reduce mortality in patients with CKD from terminal uremia, including complications of renal replacement therapy (RRT), and the extrarenal manifestations of CKD in the first place - from heart disease morbidity.

Disorders of vitamin D homeostasis in CKD is detected at an early stage of renal failure. The majority of patients with CKD in stage III has the relative deficiency of the vitamin D_3 active metabolite - calcitriol ($1,25 (OH)_2 D_3$) in the blood. In the future, as the deterioration of renal function when the level of glomerular filtration rate (GFR) falls below $50 \text{ ml/min/1.73 m}^2$ in children and below $30 \text{ ml/min/1.73 m}^2$ in adults, an absolute calcitriol deficit develops.

CKD progression is accompanied by a decrease in the number of vitamin D receptors (VDR) and calcium sensitive receptors (CaR) of parathyroid glands with a drop of parathyroid glands sensitivity to the action of calcitriol and Ca^{2+} .

Vitamin D levels in the blood may be low in CKD patients with nephrotic proteinuria, due to loss of $25 (OH) D_3$ in the urine [1, 2].

Calcitriol inhibits parathyroid gland activity, causing a decrease in transcription and synthesis of PTH, increases the sensitivity of CaR in parathyroid gland cells, thereby blocking the mechanisms of secondary hyperparathyroidism development. In experimental studies have been shown that calcitriol deficiency may initiate of secondary hyperparathyroidism even in the absence of hypocalcemia [1, 2].

There is now evidence that the beneficial effects of calcitriol in the kidney due to an increase expression in proximal tubules of the renoprotective Klotho protein transmembrane form. [3–5]. But, as has been shown in clinical studies, intake of calcitriol is accompanied by a number of side effects:

- due to the calcium and phosphorus gastrointestinal absorption increase, rising their concentration in blood serum, which can advance the soft tissues calcification, including heart and blood vessels
- pharmacological calcitriol doses can cause damage to the vessels elastic membrane, causing inflammation
- excessive PTH suppression may transform secondary hyperparathyroidism in adynamic skeletal disease

To date, the only drug from the group of vitamin D, responsible to nephroprotective strategies, as well as prevention and treatment of secondary hyperparathyroidism is paricalcitol (Zemplar) - $1,25 (OH)_2 D_2$ - selective active metabolite of vitamin D, whose structure is modified of the side chain (D_2) and ring A. Paricalcitol selectively induces the expression of VDR (S-VDRA) genes in parathyroid glands by suppressing of IPTG secretion, do not activates of VDR in the intestine and has little effect on bone resorption, and therefore less likely causes hypercalcemia than non-selective active metabolite of vitamin D [1]. In contrast to calcimimetic group paricalcitol has expressive pleiotropic effects, due to of which risk of cardiovascular events, cancer reduces [11].

There are two formulations of the drug - a capsule for 1, 2 and 4 mcg and ampoule for 1 ml (5 micrograms). Capsules are indicated for the prevention and treatment of secondary hyperparathyroidism that develops in CKD III, IV and V stages, and ampoule - in CKD stage V [2, 6].

PATIENTS AND METHODS

The study included 50 patients with CKD stage III–IV. Patients were divided into 2 groups. The 1st group consisted of 28 patients (8 – with III and 20 – with stage IV), which was used calcitriol at the dose of 0.25 mcg/day. 22 patients (9 with III and 13 – stage IV) were included in group 2 and administered paricalcitol at a dose 1 mcg per day (tabl. 1). Calcitriol and paricalcitol with nephroprotective aim were applied when the blood level of intact parathyroid hormone (iPTH) was not below 65 pg/ml, and based on the indicators of phosphorus-calcium exchanges. The 1st and 2nd patients groups administered necessary RAS blockers, erythropoietin and iron preparations, and statins also. In 10 patients of group 1 and 12 patients of group 2 at admission and at the end of the study period common carotid arteries Doppler ultrasound was performed.

RESULTS

Prior to calcitriol and paricalcitol treatment, proteinuria was $1,3 \pm 0,5 \text{ g/day}$ in group 1 and $1,2 \pm 0,3 \text{ g/day}$ in group 2, and the PTH level – $76 \pm 18, 6 \text{ pg/ml}$ and $82 \pm 16,6 \text{ pg/ml}$ respectively (tabl. 2).

Combined calcification/atherosclerosis lesion of common carotid arteries was showed in 27,3% of group 1 patients and in 33,3% of group 2 patients. Calcitriol and paricalcitol were tolerated satisfactorily. As a result, after 3 months from the beginning of these drugs use, in initially diagnosed blood increased PTH levels patients the normalization of its contents was reached. In patients received paricalcitol, proteinuria

reducing occurred more rapidly ($p < 0,05$), while hypertension reducing to the end of 3 months was more significant ($p < 0,01$), than with calcitriol (tabl. 3).

Table 1. Distribution of patients according to stage of CKD

Patients groups	CKD III st. (GFR* 30–59 ml/min/1,73 m ²)	CKD IV st. (GFR 15–29 ml/min/1,73 m ²)
group 1, n=28 Calcitriol (0.25 mcg/day, orally)	8	20
group 2, n=22 Paricalcitol 1 mcg/day, orally)	9	13
altogether	17	33
in total	50	

* – GFR – glomerular filtration rate

Table 2. Effect of calcitriol and paricalcitol treatment on the concentration of IPTG in blood and daily proteinuria in patients with CKD III–IV stages due to systemic diseases

Index	1 group		2 group	
	before treatment	after 6 months of calcitriol treatment (0.25 mcg/day)	before treatment	after 6 months of paricalcitol treatment (1 mcg/day)
iPTG (pg/ml)	76+18,6	66+12,2	82+16,6	60+14,4*
Proteinuria (g/day)	1,3+0,5	0,8+0,32	1,2+0,3	0,3+0,21*

The differences were statistically significant: * – $p < 0,05$

Table 3. Comparative analysis of the blood pressure control effectiveness with use of ACE inhibitor (monopril) in combination with calcitriol or paricalcitol on LVMI regression

Index	Δ Arterial pressure (mm Hg)		Δ Left ventricular mass index	
	systolic	diastolic	men	women
Monopril + calcitriol (0,25 mcg/day)	(-) 20,1+2,89	(-) 11,9+1,82	(-) 6,6+3,14	(-) 5,9+3,58
Monopril + paricalcitol (1 mcg/day)	(-) 23,3+3,21	(-) 12,8+2,03	(-) 20,6+4,25**	(-) 21,3+3,86**

The differences were statistically significant: * – $p < 0,01$

During the same period among 12 patients in group 2 at 4 with diagnosed arteriosclerosis/calcification, episodes of hypercalcemia, as well as the progres-

sion of atherosclerosis/calcification were not identified. In contrast, among patients treated with calcitriol, hypercalcemia episodes were recorded in 21,4% and in 3 diagnosed of arteriosclerosis/calcification patients during the screening was revealed its progression (tabl. 4).

Table 4. The frequency of arterial calcification in patients with CKD stage III–IV, depending on the previous therapy

Treatment	The frequency of atherosclerosis/calcification progression in%	
	CKD III st. (GFR 30–59 ml/min/1,73 m ²)	CKD IV st. (GFR 15–29 ml/min/1,73 m ²)
Calcitriol (0,25 mcg/day)	12,5%	15%
Paricalcitol (1 mcg/day)	0%	0%

DISCUSSION

Antiproteinuric effect of paricalcitol was confirmed in 3 double-blind, randomized, placebo-controlled studies including 220 patients with CKD III–IV stages and hyperparathyroidism. By the end of 24 weeks, proteinuria reduction was observed in 51% of patients treated with paricalcitol and 25% of patients receiving placebo ($p=0,004$). Antiproteinuric effect of paricalcitol was independent of patients' age, sex, race, whether they have concomitant diseases (diabetes, hypertension) [2]. Reduction of PTH level by 30% was noted in 91% of paricalcitol treated patients, compared with 13% of patients receiving placebo ($p<0,001$). At this reduced level of IPTG <110 pg/ml was observed in 75% of patients in the group treated with paricalcitol and 12% in the placebo group [1].

It is established, paricalcitol corrects intraglomerular hypertension by inhibiting of RAS, decreases the synthesis of renin, ET-1 receptors and inhibits of mesangial cell proliferation, podocyte hypertrophy, and increases of megalin and nephrin expression. When paricalcitol combined with losartan achieved the most pronounced nephroprotective effect. Repeated morphological study of kidneys at 6 months of treatment was revealed slowing development of glomerulosclerosis and tubulointerstitial fibrosis. The high efficiency of this combination is explained by a more pronounced decline prorenin in blood with suppressed of its cellular receptors expression, as well as paricalcitol immunomodulatory effects on T-lymphocytes [1].

The experiment provided evidence that paricalcitol increases the expression of Klotho in kidney [4, 5]. Therefore, the paricalcitol use in CKD can be effective for inhibiting of renal disease progression. However, further clinical investigations require to confirm this hypothesis

Cardioprotective effect of paricalcitol shows LVH and heart failure regression leading to reduce of mortality in CKD predialysis and on regular hemodialysis (GD) stages. In the retrospective 3-year analysis of paricalcitol treatment outcomes of 67 000 dialysis patients, survival rate was 16% higher when compared with calcitriol treated patients [6, 7]. Indicated improvement of survival rate did not correlate with the duration of GD sessions, not depend on the level of calcium, phosphate and lipids and was mainly related to the more rapid suppression of PTH secretion, the molecular mechanisms of arteries calcification, inhibition of the RAS, reduced expression of proinflammatory cytokines in the myocardium and vascular endothelium by paricalcitol. [8–10].

High efficiency of perindopril and indapamide MB combination has been demonstrated in 4-year multicenter ADVANCE study in the group, which included more than 11,000 patients with insulin independent diabetes mellitus with use of severe hypertension and glycemic control [8]. In this case there was a significant decrease in total and cardiovascular mortality, and complications caused by micro- and macroangiopathy. The incidence of microalbuminuria (proteinuria) and the progression of CKD decreased more than 20%. To enhance the antiproteinuric effect the authors recommend a combination of ACE inhibitor + indapamide MB + statin + epoetin + paricalcitol.

Paricalcitol with nephroprotective aim must be appointed at the level of intact blood PTH is not below 65 pg/ml, and based on indicators of phosphorus-calcium exchange [10].

Data based on three prospective, randomized, multicentral trials show the effective suppression of IPTG secretion by paricalcitol, as well as reducing of the bone alkaline phosphatase isoenzyme activity and osteocalcin content in the serum, due to reduced bone resorption [11–14].

Serum concentrations of calcium and phosphorus due to paricalcitol using did not differ from those in the placebo group [7].

As the results of the placebo-controlled studies [1, 2, 7] the frequency of adverse events in groups of CKD patients treated with placebo and paricalcitol did not differ significantly (table 5).

Thus, the use of paricalcitol in predialysis CKD stages with hyperparathyroidism is associated not only with normalization of IPTG and alkaline phosphatase, but also a significant decrease in daily proteinuria, and LVH and chronic heart failure (CHF) regression. At the same cardioprotective and antiproteinuric effects of paricalcitol do not depend on the PTH production [14]. Paricalcitol (Zemlar) selectively affects the

Table 5. Comparative analysis of the complications frequency in patients with CKD group when paricalcitol and placebo applying (summarized results of the placebo-controlled trials)

Adverse events	Paricalcitol (n=62) %	Placebo (n=51) %
Common symptoms:		
Chill	5	2
Malaise	3	0
Fever	5	2
Flu-like symptoms	5	4
Edema	17	10
Circulatory system:		
Tachycardia	13	10
Digestive system:		
Dry mouth	3	2
Nausea	13	10
Vomiting	8	6
Aggravation of peptic ulcers	5	2
Nervous system:		
Dizziness	5	2

gene expression of cell proliferation and differentiation regulators, molecular angiogenesis mediators.

The results of research offers promise for wider use of paricalcitol (Zemlar) drug, not only for the treatment of secondary hyperparathyroidism in dialysis patients but for nephro- and cardioprotection in patients with CKD.

CONCLUSION

The application of paricalcitol at the predialysis stage of CKD with hyperparathyroidism is accompanied not only with normal levels of PTH, but also a significant decrease in daily proteinuria and hypertension.

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CLINICO-LABORATORY PARALLELS BETWEEN THE STATE OF LIPID SPECTRUM IN PREGNANT WOMEN WITH OVERWEIGHT AND PATHOLOGY OF THE FETOPLACENTAL SYSTEM: PRELIMINARY DATA

N.A. Negrusha

S.M. Kirov Military-medical academy, Saint-Petersburg, Russia



Nadezhda A. Nergusha
MD, gastroenterologist,
gastroenterology department
negrunya@mail.ru

Abstract

The article presents the data on the degree of influence of dyslipidemia on the state of fetoplacental complex. It was found that the excess production of low-density lipoproteins in mothers with nutrition-constitutional obesity is a risk factor for the formation of the fetus macrosomia. One of the possible causes of pathological dyslipidemia can be intra-hepatic cholestasis of the pregnant. The data obtained can be used in the practical work of the obstetrician-gynecologists, as well as therapists-practitioners in the field of extragenital pathologies of pregnant women.

Keywords

pregnant women, exogenous obesity, dyslipidemia, fetal macrosomia.

INTRODUCTION

The fundamental mechanism of physiological course of pregnancy consists in adequate restructuring of the endocrine system of the mother, which, in particular, is realized due to the formation of the placenta. The placenta secretes many different metabolic hormones – human chorionic gonadotropin, progesterone, estrogen, placental lactogen; the synthesis of glucocorticoids, thyroid hormones, with contrinsular and lipolytic action also increases. All this leads to the formation of transitive tolerance to glucose violations and dyslipidemia of a pregnant woman. In women with normal body mass these metabolism changes are physiological in nature and aimed at the adequate provision of a fetal with energy and plastic material. However, in case of mothers' overweight gestational restructuring of metabolism occurs on a background of already existing carbohydrate and lipid metabolism disorders, which, undoubtedly, leads not only to the aggravation of metabolism pathology in women, but also to various kinds of violations of fetoplacental complex.

RESEARCH OBJECTIVE

The purpose of this study was to explore some features of metabolism change in pregnant women with

excessive body mass, as well as to evaluate their effect on the course of pregnancy and fetal development.

MATERIAL AND METHODS OF RESEARCH

The study included 45 pregnant at the later time period (the average gestational age $32,2 \pm 4,5$ weeks), and 143 women in childbirth (the average term of pregnancy at the time of delivery was $39,8 \pm 1,3$ weeks), who were in-patients of the clinic of obstetrics and gynecology of the Military-medical academy named after S.M. Kirov during from 2005 to 2010. The average age of the surveyed was $28,2 \pm 4,9$ years. The main criterion for sampling was the presence of the mother's nutrition-constitutional obesity of different degree. The degree of obesity was assessed with the body mass index (growth, $\text{cm}^2/\text{weight}$, kg), calculated on the basis of the size and weight of the mother, specified in the prenatal record at the time of the registration in the antenatal clinic (the average term of pregnancy $11,2 \pm 2,4$ weeks). The comparison group included 20 pregnant women and 19 practically healthy women of a representative of the age and the period of gestation.

All the pregnant women were analyzed from the point of their height, weight, concomitant therapy and

obstetric pathology diagnosed during this pregnancy, indicators of biochemical blood tests (total cholesterol, lipidogram, total protein, bilirubin, glucose, urea, ALT, AST). Additional parameters for the analysis in the group of mothers were complications developed in the period of confinement, and the anthropometric parameters of the newborn.

Statistical processing of the obtained data was performed on a personal computer using the package of applied programs "STATISTICA 8.0 for Windows".

STUDY RESULTS

The undertaken statistical analysis showed that the most significant changes in the groups of pregnant women and maternity cases concerned the laboratory indicators of biochemical blood tests, reflecting the state of metabolic processes. Thus, the estimate lipidogram revealed significant differences in the level of total cholesterol both in the group of pregnant (6.73 ± 1.4 mmol/l vs 5.21 ± 1.5 mmol/l in the control group), and in the group of mothers with overweight (8.48 ± 1.4 vs 7.06 ± 0.9 mmol/l in control group). A more detailed assessment of the level of cholesterol depending on the body weight of pregnant and women in childbirth, it was established that these differences concerned women with II degree of obesity and more. The degree of hypercholesterolemia correlates with the increase in weight of the newborn ($r=0.27$, $p<0.001$) and, respectively, with the increase of frequency of birth of children with body weight more than 4,000 grams ($r=0.45$, $p<0.05$).

The study of lipoprotein blood plasma subclasses showed that it was the level of low density lipoprotein that increased in the physiological course of pregnancy, compared with the established reference values for the Russian population outside pregnancy, while the concentration of lipoproteins of very low and high density almost did not change. However, in the case of the mother with II degree obesity, low-density lipoproteins significantly exceeded the average values obtained in the group of practically healthy women, $p<0.05$ (fig. 1). With the increase of the level of low density lipoprotein, as in the case of cholesterol, combined with the formation of macrosomia of the fetus and newborn ($r=0.25$, $p<0.05$ and $r=0.21$, $p<0.02$, respectively).

It is important to note here that the level of venous blood glucose, defined in pregnant women on an empty stomach, was not significantly different in the investigated groups from the relevant comparison group. Thus, the present data make it possible to formulate the assumption that the mass of the fetus is significantly affected not only by the level of glucose in the mother, but also by the content of low-density

lipoprotein, which, in particular, through transition into free fatty acids, are actively used by the fetus as a source of energy and plastic material. At the same time, excess synthesis of low-density lipoproteins is a negative factor, which can lead to the formation of the fetus macrosomia.

Among the factors that exacerbated the dyslipidemia, besides the state of transient hyperinsulinemia on the background of tolerance to glucose violations, was developing intra-hepatic cholestasis of the pregnant. This was also confirmed in the course of this study: a positive correlation between the level of direct bilirubin, alkaline phosphatase and concentration in the blood plasma total cholesterol, as well as low density lipoproteins ($p<0.05$) was revealed. However, a significant difference between the groups which could enable to highlight the reference values of the liver functions, as one of the components of the stratification of the risk groups of the pregnant according to the possibility of pathological dyslipidemia wasn't revealed.

In addition to the fetus macrosomia, gestosis of different degree of intensity, spontaneous abortion, preterm birth, and intrauterine fetal hypoxia developed significantly more frequently in women with overweight compared with women with normal body weight. The incidence of preterm birth correlated with the level of low density lipoprotein ($r=0.24$, $p<0.05$). It is interesting to note that according to the statistical analysis, the frequency of the preeclampsia of the contrary was less than in groups with high cholesterol levels.

Thus, the existence of a women's nutrition-constitutional obesity of II degree and more is an extremely negative factor from the point of view of the forecast of the physiological course of pregnancy. At the same time, assessment of the distribution of the frequency of occurrence of obesity in young women has shown that it is at the age from 25 to 30 that women most frequently demonstrate the second degree of obesity, i.e. at the age reproductive activity of women.

DISCUSSION OF THE STUDY RESULTS

Dyslipidemia with a predominance of very low density lipoproteins, developing in women with normal body weight, is a physiological process. However, in case of the mother's nutrition-constitutional obesity of II degree and more the physiological process acquires a pathological character. It seems that in case of hyperproduction of low-density lipoproteins, even if the level of the mother's blood serum glucose remains within the normal limits, the fetus receives an excessive amount of energy and plastic material, which ultimately leads to the formation of the fetus macrosomia.

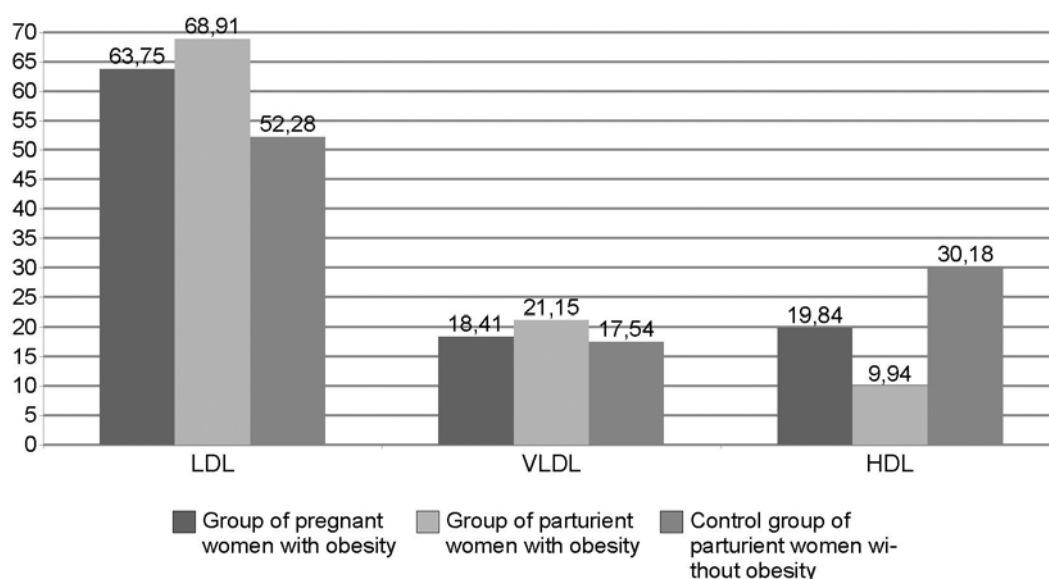


Figure 1. The average of the level of low density (LDV), very low density lipoproteins (VLDL) and high density lipoprotein (HDL) in groups of pregnant and parturient women with exogenous obesity of the second degree.

Probably permanent excessive content in the blood serum low-density lipoproteins is a factor in the development of spiral vessels of the uterus atheromatous uterus, which creates conditions for the development of chronic fetal hypoxia, which increases the risk of premature birth. However, this theory requires further study.

There are many factors that lead to a change in blood serum lipid composition in pregnancy, but the main reason is still considered a hyperinsulinemia on the background of the gradual development of tolerance to glucose violations. At the same time one should not underestimate the contribution of functional changes of the hepatobiliary system in the form of intrahepatic cholestasis of pregnant women. As it is known that hyperestrogenemia, leading to disruption of the production of bile acids, is currently recognized as the alleged pathogenetic factor of development of gestational cholestasis. At the same time it is in the fatty tissue that aromatization of androgens to estrogens takes place. As a consequence of the fat tissue excess the production of estrogen, which aggravates cholestasis, which in its turn contributes to the formation of pathological dyslipidemia, increases.

Thus, from the abovementioned, we can conclude that obesity is not only a present day problem, but a global problem of the future as well, as it is this disease that, in the view of its scale, makes a significant effect on the reproductive function of women and in the future may be a direct cause of the birth rate decline.

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CAPABILITIES OF INFRARED THERMOMETRY AND THERMOGRAPHY IN ACUTE AND CHRONIC CEREBRAL CIRCULATION DISTURBANCES

J.P. Potekhina Prof., A.V. Gustov Prof., I.A. Gafiatullin, M.V. Golovanova

*Nizhny Novgorod State Medical Academy, Russia
LLC CEM-ThermoDiagnostics, Nizhny Novgorod, Russia*

INTRODUCTION

Currently, one of the main problems of public health is cerebrovascular pathology – the third cause of death and one of the reasons of disability of people in many countries. According to WHO experts, in the future the number of cerebrovascular diseases will be merely increasing due to ageing of population and the increase of such risk factors as arterial hypertension, diabetes mellitus, hypercholesteremia, smoking, obesity, hypodynamia, etc [1].

Chronic cerebral circulation disturbances number the major part (96%) in the structure of cerebrovascular diseases. The frequency of chronic cerebral ischemia grows with the increase of years. Cognitive disorders of vascular genesis are revealed in 5–22% of elderly. In autopsy various vascular diseases are found in a third of elderly people [2]. At the same time, almost half of all the cases of chronic cerebral ischemia that can lead to stroke is recorded in working population. [1]. At early stages, chronic cerebral ischemia can be asymptomatic or with minimum clinical presentation, so patients do not turn to doctors for duly help and do not receive the treatment required. For the same reason strokes often occur against the background of “visible health”. Stroke incidence rate is increasing in people of working age; and stroke is a leading cause of disability of population. Taking into account medical, social and economical aspects of the spread of cerebrovascular pathology, WHO experts have declared a stroke to be a global epidemic threatening national safety. As a whole, all these factors necessitate to prepare a package of preventive measures, modern diagnosis of cerebrovascular diseases holding a ranking place [3, 4].

Patients who survived a stroke or a transient ischemic attack are frequently nervous about the possibility of attack repeat and enquire what they are to do. In 10% of patients with transient ischemic attacks hospitalized by emergency, a stroke develops within 90 days even if traditional therapy is administered [5]. Reanalysis of findings of Oxfordshire Community Stroke Project has showed the risk of stroke to achieve

12% in the first 90 days [6]. To reach a maximum effect, the treatment is to be started as soon as possible, as well as the monitoring of patient's condition in the course of treatment.

According to diagnostic value, neuroimaging techniques – computer tomography or magnetic resonance imaging – head the list in cerebrovascular pathology diagnosis, as they enable to reveal cerebral organic changes of vascular genesis [7; 8]. However these methods do not give adequate information concerning the state of cerebral circulation, therefore they have limitations in monitoring patients' condition and in the control of treatment effectiveness. Therefore, there are needed methods of control of the level of cerebral blood supply, easy and available to people that could estimate the effectiveness of preventive and therapeutic intervention in chronic and acute cerebral circulation disturbances.

Circulation failure is one of the causes of skin temperature changes. Disturbed arterial circulation in internal carotid artery that supplies the brain is known to be manifested in the reduction of skin temperature of the orbital interior angle and medial superciliary area [9].

The aim of the work was to study the capabilities of infrared thermometry and thermography in cerebrovascular pathology.

METHODS AND MATERIALS

There have been examined the patients with acute and chronic disturbances of cerebral circulation:

- 61 patients with chronic cerebral ischemia, among them 22 men aged 51–79 yrs (median age: 59 years old) and 39 women aged 46–85 yrs (median age: 60 years old), and 40 of them have been treated in in-patient department within 3 weeks;
- 60 patients with ischemic stroke, aged 24–73 yrs (median age: 53 years old) in peracute and early rehabilitation period, and 33 men and 27 women of them have been treated in a specialized hospital within 3 week followed by rehabilitation period in specialized country in-patient department for 24 days.

The control group consisted of apparently healthy 60 people – 32 men aged 17–68 yrs (median age: 27 years old) and 28 women aged 17–62 yrs (median age: 34 years old).

All the patients underwent a complex of the investigations required. Besides, infrared thermometry and thermography using personal thermograph CEM®-ThermoDiagnostics was used on admission to hospital and then every week to the end of treatment. The procedure was carried out in the morning before the meal, at room temperature, in the absence of air flow, away from heat. Within 10 minutes before the examination the patients were lying or sitting in a comfortable armchair.

Personal thermograph CEM®-ThermoDiagnostics is a hardware and software complex (Fig. 1). It includes infrared thermometer that measures the intensity of thermal radiation in any areas of the body and transfers information to the computer, and “CEM® Thermo Image Bio” program (State Registration Certificate No. 2011611309 dated 09.02.2011) that makes thermograms on the photos of the patient’s areas of concern or on the 3D model of human body.



Fig. 1. Personal Thermograph CEM®-ThermoDiagnostics

The temperature was measured in the areas that reflex the blood flow level in internal and external carotid arteries, as well as in vertebrobasilar system:

- central frontal point – along the medial line of the forehead, 4.5–5.5 cm above the level of the inner angle of the eye;
- medial superciliary points – 3–3.5 cm above the inner angle of the eye;
- medial orbital points – immediately above the inner angle of the eye;
- temporal points – 5–6 cm above the external auditory canal;

– occipital points – immediately below greater occipital tubers.

Statistical processing was carried on using methods of nonparametric statistics, by means of the program Statistica 7.0. To find out the differences between the samplings, there were used Wilcoxon criterion for paired comparison and Mann-Whitney U-test. Critical level of significance in testing statistical hypotheses was taken equal to 0.05.

RESULTS AND DISCUSSION

The analysis of temperature measurements of healthy people heads showed that normally there is spread of absolute values of temperature of the head surface within the range 26.8–35.6° C, and temperature asymmetry in representative points on the head is no more than 0.6° C (Table 1).

Table 1. Thermometric values in representative points on the head of apparently healthy people

Name of the point	Temperature values, °C	Temperature asymmetry, °C
Central frontal point	29.4-35.2, median 33.6	
Medial orbital point	29.0-35.2, median 33.6	0-0.6, median 0.2
Medial superciliary point	29.6-35.0, median 33.6	0-0.6, median 0.2
Temporal point	27.2-35.6, median 33.6	0-0.6, median 0.2
Occipital point	26.8-35.2, median 32.7	0-0.6, median 0.2

In patients with chronic cerebral ischemia there is spread in absolute temperature values on the head within the range 26.0–35.6° C, and in all the representative points it is statistically significantly lower than in healthy people; temperature asymmetry on the head ranges from 0 to 4.2° C, and in all the representative points – statistically significantly higher than in healthy people (Table 2). Figure 2 shows a frontal thermogram of a patient with chronic cerebral ischemia.

The results of treatment in all the patients were estimated as good. The analysis of dynamics in the course of chronic cerebral ischemia treatment demonstrated that:

- there was temperature increase in all treated patients at least in one representative point;
- there was no temperature decrease in any patient within the treatment process;
- the dynamics of the temperature measured was irregular and asymmetric in various representative points;
- the increase of temperature at least in one representative point in the majority of patients started after 2 weeks’ treatment in hospital;

- more frequently the temperature rose in medial superciliary and occipital points, therefore, just in these points the temperature is to be controlled first of all.

Table 2. Thermometric values in representative points on the head of patients with chronic cerebral ischemia

Name of the point	Temperature values, °C	Variations from healthy	Temperature asymmetry, °C	Variations from healthy
Central frontal point	31.0-34.2, median 32.9	p=0.005		
Medial orbital point	30.4-34.6, median 33.2	p=0.01	0-1.8, median 0.2	p=0.04
Medial superciliary point	30.2-34.4, median 32.7	p=0.001	0-0.8, median 0.4	p<0.001
Temporal point	26.0-35.6, median 30.1	p<0.001	0-3.8, median 1.0	p<0.001
Occipital point	26.2-35.6, median 30.4	p<0.001	0-4.2, median 0.8	p<0.001



Fig. 2. Frontal thermogram of the patient with chronic cerebral ischemia superimposed on 3D cranial model.

Temperature values of skin integument of the head in ischemic stroke differ slightly in various periods of the disease. The temperature rises significantly statistically in early rehabilitation period in the occipital point and in the area of medial orbital edge (Table 3), that can be indicative of the establishment of flow in internal carotid artery and vertebrobasilar system. Temperature asymmetry in this case is not high on the average, though in some patients it reaches 2.4° C. In different periods of the disease the temperature asymmetry does not change significantly statistically.

The results of treatment in all the patients were estimated as good. The temperature of the head skin in representative points in 50% of cases began to increase even in two weeks after the treatment had started, though statistically significant changes in ischemic stroke occurred only after three weeks of treatment in hospital. In aggravation there was the increase of temperature asymmetry in various points that can be regarded as unfavourable prognostic sign.

The analysis of dynamics in acute period of cerebral ischemia demonstrated that:

- there was temperature increase in all treated patients after three weeks of treatment initiation at least in four representative points on the head;
- there was no temperature decrease in any patient within the treatment process;
- the dynamics of the temperature measured was irregular and asymmetric in various representative points;
- more frequently the temperature rose in medial orbital, medial superciliary and temporal points, therefore, just in these points the temperature is to be controlled first of all.

In early rehabilitation period of treatment there was improvement in all the treated patients. The temperature of head skin practically did not change, and the goodness of fit of the treatment administered was the stability of values.

Table 3. Thermometric values in representative points on the head in stroke

Name of location	Peracute period		Early rehabilitation period		Temperature differences
	Temperature values, °C	Temperature asymmetry, °C	Temperature values, °C	Temperature asymmetry, °C	
Central frontal point	32.4-34.2, median 33.6		30.8-35.0, median 33.5		p>0.05
Medial orbital	32.0-35.0, median 33.6	0.2-1.0, median 0.4	31.6-35.8, median 34.4	0.2-2.0, median 0.4	p=0.04
Medial superciliary	31.8-34.4, median 33.4	0.2-2.4, median 0.4	30.8-35.4, median 33.8	0.2-2.0, median 0.4	p>0.05
Temporal point	31.8-35.6, median 34.4	0.2-2.2, median 0.8	31.2-35.6, median 34.4	0.2-1.6, median 0.4	p>0.05
Occipital point	29.6-35.8, median 34.0	0.2-2.0, median 0.4	31.6-35.8, median 34.6	0.2-1.4, median 0.2	p=0.02

CONCLUSION

Thus, for the first time there have been obtained temperature absolute values of head skin integument measured in infrared range in healthy people and in patients with cerebral circulation disturbances. The findings let us establish the scheme of early preclinical diagnosis of chronic cerebral ischemia and the risk of stroke, as well as recommend to use personal thermograph CEM[®]-ThermoDiagnostics to monitor the condition of patients with cerebrovascular pathology and assess the treatment effectiveness.

“CEM[®] Thermo Image BIO” program is rather simple, so it can be used by both doctors and at home – by those who care for their health and by patients or their relatives. Regular examinations are of primary importance in those who have risk factors: age (after 40), smoking, hypodynamia, the presence of arterial hypertension, diabetes mellitus and obesity.

Personal thermograph CEM[®]-ThermoDiagnostics has all the advantages of thermovision cameras: absolute safety both for patients and medical staff, noninvasive character, unlimited retest frequency, results reproducibility, ease of use. Moreover, CEM[®]-ThermoDiagnostics has the following additional advantages: availability, portability, the possibility to measure temperature with optimal accuracy in any areas of the body including hair-covered. Personal thermograph CEM[®]-ThermoDiagnostics does not need any specially equipped room.

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ZEIT IST LEBEN VOM INFARKTNETZ „HILDESHEIM-LEINEBERGLAND“ ZUM FITT-STEMI-PROJEKT

Karl Heinrich Scholz Prof. DM

St. Bernward Krankenhaus, Hildesheim, Deutschland

KOMPETENZ IN DER MEDIZIN

90 MINUTEN BIS ZUR WIEDERERÖFFNUNG

Das Akute Koronarsyndrom (ACS) ist ein bedrohliches Ereignis mit hoher Sterblichkeit. In der Regel kommt es dabei durch Einriss eines atheromatösen Plaques am Kranzgefäß mit konsekutiver Thrombusbildung zum intermittierenden oder kompletten Gefäßverschluss. Nach Klinik und Pathomechanismus unterscheidet man: 1.) ACS mit persistierender ST-Hebung oder neu aufgetretenem Linksschenkelblock (ST-Elevation Myocardial Infarction: „STEMI“) und 2.) ACS ohne persistierende ST-Hebung („NSTEMI“ und Instabile Angina pectoris). Basis für eine effektive Behandlung ist die schnellstmögliche und zuverlässige Diagnostik.

Beim ACS mit fehlenden typischen ST-Hebungen im EKG steht zunächst das Erkennen und die Risiko-Einschätzung sowie die Monitorüberwachung im Vordergrund. Dies geschieht heute in vielen Kliniken in modernen Brust-Schmerz-Überwachungseinheiten („Chest-Pain-Unit“=CPU). Beim STEMI hingegen hat die unmittelbare Einleitung einer Kausaltherapie mit schnellstmöglicher Wiedereröffnung des verschlossenen Herzkranzgefäßes oberste Priorität. Die perkutane koronare Intervention (PCI) ist dabei der Lysetherapie eindeutig überlegen. Die Leitlinien schreiben beim STEMI eine Versorgung mit PCI innerhalb von 90 Minuten nach Erstkontakt mit dem Rettungsdienst vor.

BAISISSTRUKTUR: PRÄHOSPITALES 12-KANAL-EKG UND INFARKTVERNETZUNG

Allerdings können derzeit bei den meisten STEMI-Patienten diese hohen Zeit – Anforderungen der Leitlinien nicht eingehalten werden. Durch Schaffung einer entsprechenden Basis-Struktur und durch Etablierung systematischer QM- Maßnahmen kann die Prozessqualität bei der STEMI-



Medizinische Klinik I,
Abteilung Kardiologie und Intensiv-
medizin, St. Bernward Krankenhaus
Treibestraße 9, 31134 Hildesheim
prof.dr.k.scholz@bernward-khs.de

Behandlung jedoch deutlich verbessert werden. Von grundsätzlicher Bedeutung ist die enge Einbeziehung des Rettungssystems und die Nutzung der Prähospitalphase. Zu den von den Leitlinien vorgeschlagenen strukturellen Maßnahmen gehört die Einrichtung von sogenannten Infarktnetzen.

Unabdingbar ist die Festlegung auf ein fixiertes Ablaufprotokoll für die Diagnosestellung und die Alarmierungs- und Therapiekette innerhalb einer Herzinfarktversorgungseinheit. Wichtige Ziele dabei sind: Schnellstmögliche STEMI-Diagnose, das heißt systematisch prähospital 12-Kanal-EKG, gezieltes Umgehen der Nicht-Interventionsklinik und systematisches „Bypassen“ der Notaufnahme der Interventionsklinik mit Direktübergabe durch den Rettungsdienst im Katheterlabor.

DAS FITT-STEMI-PROJEKT TESTPHASE IM HERZINFARKTNETZ HILDESHEIM – LEINEBERGLAND

Ein sehr wirkungsvolles Instrument zur Verbesserung der Behandlungszeiten ist die Etablierung eines standardisierten Qualitätsmanagement- Systems. Dieser Ansatz wird aktuell in dem multizentrischen FITT-STEMI-Projekt verfolgt (Feedback-Intervention and Treatment Times in ST-Elevation Myocardial Infarction): In einer monozentrischen Testphase werden im Herzinfarktnetz Hildesheim-Leinebergland (beteiligte Kliniken: Ameos Klinikum Alfeld, Johanniter Krankenhaus Gronau und St. Bernward- Krankenhaus Hildesheim) seit 1. Januar 2006 bei allen STEMI-Patienten die Behandlungszeiten, Behandlungs- Er-

FITT – STEMI: teilnehmende PCI-Zentren



gebnisse und klinische Daten standardisiert erfasst und nach Analyse vorher definierter Qualitätsindikatoren systematisch an alle an der Akutversorgung beteiligten Systeme rückgekoppelt (gemeinsame Veranstaltungen mit Rettungsassistenten, Notärzten, Klinikärzten, Personal von Katheterlabor und Intensivstationen der beteiligten Krankenhäuser). Die Feedback-Veranstaltungen fanden im Jahr 2006 quartalsweise statt. Das Vorgehen führte im Laufe des Jahres 2006 zu einer signifikanten Reduktion der Behandlungszeiten mit Verkürzung der Contact-to-Balloon-Zeit (C2B = Zeit vom Erstkontakt mit dem Rettungsdienst bis Wiedereröffnung) um im Mittel 53 Minuten, der Anteil der Pat. mit C2B < 90 Minuten konnte dadurch von 23% auf 79% gesteigert werden (siehe auch Beitrag im niedersächsischen ärzteblatt 1/2009 vom 15. Januar 2009, Seite 19 ff.). Seit 2007 erfolgt die Datenerfassung Internet- basiert, und die Feedback-Veranstaltungen werden im Herzinfarktnetz Hildesheim-Leinebergland mit den verschiedenen Rettungsdiensten in Alfeld, Gronau und Hildesheim nur noch einmal pro Jahr durchgeführt (im jährlichen Wechsel vor beziehungsweise nach den Sommerferien). Zwar wurden die Behandlungszeiten zwischen den Feedback-Veranstaltungen kontinuierlich länger, interessanterweise wurden die Zeiten dann aber im direkten Anschluss an die jährlichen Feedbacks regelhaft wieder deutlich besser. Erfreulicherweise konnten so die sehr guten Behandlungszeiten im Mittel über die Jahre stabil gehalten werden: Der Median der Contact-to-Balloon-Zeit (C2B) liegt in der Gesamtgruppe aller im Netz behandelte STEMI-Patienten unter 80 Minuten und in der Gruppe der Patienten mit Primärtransport bei 70

Minuten, und die Behandlungszeiten im Krankenhaus („Door-to-balloon“) liegen im Median deutlich unter 30 Minuten. Über den gesamten Zeitraum gemittelt konnten im Infarktnetz Hildesheim-Leinebergland 80% der Patienten direkt im Katheterlabor übergeben werden, und so 75% der Patienten mit einer C2B-Zeit < 90 Minuten behandelt werden.

FITT-STEMI-PILOTPHASE

In der FITT-STEMI-Pilotphase wird in Form einer Machbarkeitsstudie geprüft, ob das Konzept der standardisierten Ergebnissrückkopplung auch auf andere Kliniksysteme übertragen werden kann (Teilnehmende Kliniken: Unikliniken Würzburg und Göttingen und die Kliniken in Worms, Wolfsburg, Darmstadt und Langen, sowie 29 kooperierende Nicht-PCI-Kliniken).

Die Auswertung und Vorbereitung der Feedback-Präsentationen erfolgt zentral und einheitlich für alle Kliniken, die Daten der einzelnen Kliniken bleiben anonym. Die an allen beteiligten Kliniken quartalsweise und einheitlich durchgeführten Feedback-Veranstaltungen führten innerhalb eines Jahres zu einer hochsignifikanten Verkürzung der Behandlungszeiten (Ergebnisse zur Publikation eingereicht).

FITT-STEMI-UMSETZUNGSPHASE

In der FITT-STEMI-Umsetzungsphase (FITT-STEMI-2) soll an einer großen Gruppe von weiteren PCI-Klinik-Systemen geprüft werden, ob eine solche Verbesserung der Prozessqualität mit Verkürzung der Behandlungszeiten tatsächlich auch zu einer Verbesserung der Ergebnisqualität mit Verbesserung der Prognose führt, und welche Patientengruppen davon gegebenenfalls besonders profitieren. Bisher wurden in das FITTSTEMI – Gesamtprojekt 6.500 Patienten mit akutem STEMI prospektiv eingeschlossen.

Fazit der bisherigen Ergebnisse Systematische Kommunikation führt zu besseren Behandlungszeiten und besserer Prognose bei Patienten mit akutem ST-Hebungsinfarkt.

Die Umsetzung der QM-Maßnahmen mit engster Einbindung der lokalen Rettungs- und Notarztsysteme ist flächendeckend notwendig. Die dafür nötigen Maßnahmen müssen von der Politik und der Gesellschaft mitgetragen werden, damit aus der 90-Minuten-Fiktion tatsächlich flächendeckend und vor allem dauerhaft Fakt werden kann.

COMPLICATED FORMS OF CEREBRAL STROKE, FEATURES CLINICS, DIAGNOSIS AND TREATMENT

F.I. Vasilenko Prof. MD

Ural State University of Physical Education, Chelyabinsk, Russia

Numerous clinical observations and experimental results indicate that the clinical manifestations, course and outcome of stroke (cerebral and acute myelogenous circulatory disorders) depend not only on its nature, severity, localization process, but also to a large extent on several factors: the patient's condition before the disaster brain, concomitant diseases, as well as from the accession of complications. There is every reason to believe that complications are, in most cases, one of the reasons for a poor prognosis of stroke or death. In particular, it may indicate that there is not always a parallelism between the size of brain lesion, its location and severity, the nature of the course and outcome of stroke. Moreover, at autopsy, often are quite large (greater than 10 mm in diameter) cystic cavity, histologically, no doubt resulting from stroke. Their walls include hemosiderin, indicative of hemorrhage. At the same time an objective history of the disease do not meet the clinical manifestations (not recorded a stroke or traumatic brain injury). A neurosurgical manipulation on the brain, sometimes with removal of its vast areas on various pathological processes, often do not cause corresponding disturbances, neurological symptoms. This fact is explained, despite the specificity and complexity of the morphology and function of the nervous system, in practice large compensatory capacity of the brain, it has so-called "silent zones".

Cerebral stroke is a complication of the disease or pathological process (hypertension, atherosclerosis and their combination, etc.), significantly alters the clinical presentation and course of illness, which caused acute stroke. After catastrophe cerebral it becomes a major pathological process in the body, which required a different therapeutic and diagnostic, medical, social and other therapeutic measures. It is not accident, in the WHO ICD-10 cerebrovascular diseases (CVD) became an independent nosological form and have separate rubric.

Violations of neurological function in CVD lead to the breakdown of regulation of the organs, body systems and their interactions. Prerequisites and conditions create a favorable environment for the development of other pathological processes that complicate CVD. Thus, develop "complications of complications".

Criteria of what symptoms are direct manifestations of stroke or its complications not yet developed. For example, seizures, cardiovascular disorders, pneumonia, bleeding in the infarction zone, hemorrhage or infarcts in the brain and meninges, topically or by the time criteria not connected with the main focus.

To this issue has not paid attention in modern neuroscience in most literature sources. Most authors consider only such processes as complications of a stroke, few of them attached importance to the study of the pathogenesis and characteristics of the mutual influence of possible treatment of a patient with such a course of stroke. However, in many cases, these complications of stroke can complicate diagnosis, differential diagnosis of stroke, treatment and prevention of complications.

Apparently, quite rightly should be attributed to complications of stroke and other forms of stroke pathological processes associated with the pathogenesis of stroke (according to the theory nervism), but are not required for its expression and localization of this form of brain damage. It is clear that that emphasizes complications of stroke significantly increasing the severity of the disease and can alter its clinical manifestations, course and worsen prognosis, but also requires further specific measures at different stages of treatment and rehabilitation of the patient. Acute stroke with its complications should be considered as a qualitatively different form of the disease complicated by stroke.

In practice, the complicated forms of stroke is not differ from standard approaches in diagnosis, treatment and rehabilitation, and adverse for him and death are, in most cases, due to his difficult character.

Complicated forms of stroke caused by development of the following pathological processes (Table 1).

The concept of complicated stroke remains poorly known, is not undisputed. For example, cardiologists are studying complicated forms of myocardial infarction, and it is possible to achieve positive results in working with patients in many roles.

Great difficulties represents in the differential diagnosis of symptoms and complications. For example, a seizure is often one of the first significant signs of subarachnoid hemorrhage and its recurrence may be

Table 1. Pathological processes caused by complicated forms of stroke

1.	Pronounced cerebral edema, which has no correlation with the nature, size of brain lesion and can develop in the absence of a macroscopic lesion. Perhaps as a result of diffuse axonal lesions of the hypoxic brain
2.	Secondary dislocation neurological syndromes
3.	Hemorrhage or hemorrhagic impregnation in the infarct zone
4.	Infarct of the brain associated with the focus of hemorrhage
5.	Secondary hemorrhagic or ischemic lesions, not topically related to the primary main focus
6.	Rheologic and blood coagulation changes, that are not the direct consequence of CVD: a disseminated intravascular coagulation syndrome (DIC), often manifested thrombus
7.	Aseptic inflammatory syndrome
8.	Progressive autoimmune syndrome, especially in chronic CVD
9.	Epileptic syndrome
10.	Cognitive impairment
11.	Progressive dementia
12.	Neuro-degenerative syndromes, early and late cachexia, decubitus, anorexia, bulimia.
13.	Early and late contracture of the muscles
14.	Internal organs and systems impairment: heart attacks, cardiac arrhythmias, persistent malignant hypertension, pulmonary-heart disease, disorders of the urinary system and others.
15.	Infections and inflammatory processes: pneumonia, exacerbation of chronic infections and inflammatory processes
16.	Mielo-, radiculo-, plexo-, neuropathy
17.	Different processes recur, progress, exacerbate in the body

due to recurrent hemorrhages, which often observed in intracranial arterio-venous malformations. Recurrent seizures, caused by other factors should be considered as a complication of meningeal hemorrhage, which can subsequently be transformed into epileptic disease (even when vascular malformation healed). During predisease period patient may be a potential epileptic, and may be triggered a lot of pathological processes. We should consider this fact in the diagnosis of complicated forms through an additional examination of patients.

The above discussion highlights the complexity of the selection, diagnosis and study of complicated forms of CVD. However, in practice there is a need to consider this aspect in the treatment and rehabilitation of patients with these forms of the CVD.

The clinical signs of complicated forms of CVD are:

- Heavy progressive impairment of any function of the nervous system with a poor prognosis requiring intensive care and even reanimation measures. Complicated forms occur 3 times more often in severe than moderate stroke.

- The presence of concomitant diseases: diabetes, postinfarction heart failure, cardiac arrhythmias, cardiomyopathy (dilated or hypertrophic), pulmonary pathology, a history of CVD.
- Localization of the focus in the deep structures of the cerebral hemispheres, vertebrobasilar pool, spinal cord.
- Vascular lesion of tonsillar-limbic-reticular system of the brain.
- Mismatch of the volume, nature and location of the lesion of the nervous system on the one hand with clinical severity on another. Sometimes neurovisualization shows that in small focus localized in a meaningless functional area of the brain stroke may be severe.
- Significant aggravation of following syndromes: respiratory rate, depth, rhythm violations, cardiovascular failure, pulmonary edema, aggravation of neurological, especially cerebral manifestations (impaired consciousness from a coma to stupor), hyperkinesia and other symptoms and syndromes.
- Deterioration in homeostasis: DIC syndrome, thrombohemorrhagic manifestations, systemic or local microcirculation in different vessels.
- Hemorheological changes.
- Increasing of the concentration of products of lipid peroxidation, increase anaerobic glycolysis, nitric oxide metabolites fluctuation, active neuroendocrine substances.
- Sudden deterioration of the patient, the severity of cerebral and focal manifestations of non-recurrent episode (recurrent vascular process in the nervous system).

Wide polymorphism of clinical manifestations, course, outcome CVD probably more due to the formation of complicated forms of CVD that occur in at least 15–30% cases at different stages of the stroke. We can distinguish several features of clinical manifestations and course of complicated forms CVD.

Complicated forms CVD can often be characterized by unexplained sudden deterioration of the patient, exacerbation of neurological focal cerebral and somatic system and organ failure that lead to a sharp deterioration of the patient. In practice this is often due to the aggravation or recurrence of the pathological process in the brain (ischemic deepening of the process, re-bleeding, etc.). In many cases, complication is a reason for the revision of the initial diagnosis and provide additional examination of the patient.

Thus, the complicated forms of CVD are characterized by features of pathogenesis of pathological processes, clinical manifestations, hemodynamic homeostasis autonomic processes, trends, outcomes and close relationship to primary vascular at different stages of the disease.

STUDY ABOUT INFLUENCE OF OSTEOPATHIC TREATMENT ON LIFE QUALITY OF PATIENTS WITH CHRONIC PAIN SYNDROME IN LUMBUS AND LOWER EXTREMITIES

G.V. Yakovets¹, S.V. Novoseltsev²

¹St. Petersburg State University, Medical Faculty, Institute of Osteopathy, St. Petersburg, Russia

²St. Petersburg Medical Academy of Postgraduate Studies, Institute of Osteopathic Medicine, St. Petersburg, Russia

INTRODUCTION

Over 50% of people of working age have in the course of life episodes of pain in the back, which have nothing to do with inflammatory, systemic, oncologic or metabolic diseases. Changes caused with lumbar osteochondrosis are detected with X-ray in 50% of people over 50 years old. Moreover, society and patients incur big economic and financial losses because of frequent hospitalizations and long periods of temporary disability. Nowadays, there are different methods of treatment for such conditions, including manual therapy. However, there is still a relevant problem – proper complex assessment of efficiency, including long-term efficiency, of any treatment method or complex of therapeutic methods.

Lately, interest for assessment of not just medical results of treatment, such as manifestations of a disease or their absence, but assessment of social and psychological consequences of a disease, that is how comfortable a patient can feel in the environment, including society, has increased considerably.

There are five principal generally recognized treatment assessment categories (G.I. Nazarenko, I.B. Geroyeva, A.M. Cherkashov, A.A. Rukhmanov, 2008): vertebral column functions; medical condition in general (“quality of life”); presence or absence of a disease; work incapacity; a patient’s satisfaction with the result

Quality of life (QL) is an integral feature of physical, psychic, emotional and social functioning of an individual based on his/her subjective perception.

In this work a comparative analysis of qualitative results of osteopathic and traditional treatment of the patients with pain syndrome in lumbus and lower extremities is given. Within the limits of the analysis it was taken into consideration that quality of life is, first of all, determined by the way the patient assesses degree of his/her satisfaction with various aspects of his/her life in their connection with real or expected



Gennady V. Yakovets



Svyatoslav V. Novoseltsev, MD

Abstract

Osteopathic treatment of the patients with pain syndrome in lumbus and lower extremities definitely results in improvement of physical as well as psychological elements of quality-of-life index.

Keywords

chronic pain in lumbus and lower extremities, osteopathic correction, life quality

changes caused with the disease and its consequences and related to medical supervision and treatment.

On the basis of these ideas it was decided to prove that osteopathic correction is an efficient, expedient and preferable method of treatment of this pathology by way of studying medical parameters of a patient’s quality of life.

RESEARCH OBJECTIVES

to assess how osteopathic treatment influences quality of life of the patients with chronic pain syndrome in lumbus and lower extremities.

RESEARCH TASKS

1. To elaborate criteria for selection of patients for the research and form an index group and control group.
2. To elaborate the research design including algorithms of osteopathic diagnostics and treatment.

3. To compare changes in quality of life of patients with chronic pain syndrome in lumbus and lower extremities within the limits of osteopathic treatment and within the limits of pharmaceutical treatment.
4. To assess durability and stability of the assumed improvement of quality of life of the patients after treatment completion.

RESEARCH MATERIALS AND METHODS

We have selected 30 patients for the research. The index group consisted of 15 males at the age from 35 to 55 years old (average age made up $45,5 \pm 1,7$) with lumbodinia/lumbar ischialgia syndrome without associated neurologic symptoms of "prolapse". The criteria according to which patients were included in the group or excluded out of it are shown in Table 1.

Control group comprised 15 male patients from 35 to 53 years old (average age $43,1 \pm 1,3$) selected in the same way. Information about the participants and characteristics of the groups is given in Table 2.

Before the treatment all the patients were examined according to the act (Table 3).

Moreover, index group patients were interviewed from the viewpoint of osteopathy, osteopathic anamnesis was collected and primary osteopathic diagnosing was done.

Index group patients underwent a course of osteopathic treatment comprising 6–8 therapeutic sessions according to the following scheme: 2 sessions with the break of 3–4 days between them; 2–3 sessions with the break of 1 week between them; 2–3 sessions with the break of 2 weeks between them.

Choice of methods is determined basing on the character of the osteopathic affections detected and on osteopathic dynamics.

During the osteopathic treatment course the patients were offered to abstain from other kinds of treatment. Those who had to keep physically active were allowed to wear immobilizing dorsolumbar orthosis. The total length of treatment period for the index group patients made up 4–6 weeks.

Control group patients were treated in a standard way under neurologist's control, which included:

1. Limitation of motion (some patients used immobilizing dorsolumbar orthosis).
2. Individually prescribed medicines (in most cases – combination of NSAID nimesulide 200 mg/day and neuromuscular relaxant Mydocalm 300–450 mg/day in the course of 10–14 days with further intake cessation or dose decline).
3. Sacrolumbar spine massage (10 sessions).
4. Physiotherapy (individual programme was elaborated by physiatrist).

5. Remedial gymnastics according to the individual programme recommended by coach.

As soon as the treatment has been accomplished, patients of both groups underwent final examination which comprised collecting of complaints, the second neurologic inspection, and questioning within the limits of SF-36 health survey (clauses 1, 2, 4, Table 5). Index group patients passed through final osteopathic testing according to the algorithm similar to the first diagnostics. The results of the final diagnostic tests were recorded, too.

In the final round of the research, i.e. 5–6 months after the end of the treatment active phase, the patients of both groups were questioned within the limits of SF-36 health survey.

The following indexes were analyzed and compared (Table 4):

QUALITY-OF-LIFE CHANGES ASSESSMENT IN GROUPS

Quality-of-life physical element

In the index group (Table 5, Fig. 1), original integral point according to quality-of-life physical health scale (PH) of SF-36 survey made up $43,8 \pm 1,4$, while the minimal point was $18,6 \pm 4,0$ according to BP scale (pain intensity) and the maximal point – $44,7 \pm 4,7$ according to PF scale (physical functioning).

After the treatment completion PH integral point made up $51,5 \pm 1,4$, i.e. it increased by $7,7 \pm 1,5$. The most significant improvement took place according to the scale of role functioning (RP) – by $55,0 \pm 8,9$ and according to the scale of pain intensity (BP) – by $54,9 \pm 4,2$.

6 months after the treatment completion PH integral point made up $49,6 \pm 1,2$, i.e. it was still higher than the original point by $5,8 \pm 1,2$. The most significant improvement was registered according to the scale of pain intensity (BP) – by $49,8 \pm 3,9$ and according to the scale of role functioning (RP) – by $45,0 \pm 9,2$.

Fig. 1 shows that 6 months after the treatment completion average indexes according to all the scales of quality-of-life physical element came down just a little bit in comparison to the moment of the treatment completion (measuring 1) and stayed much higher than the original ones (measuring 0).

The difference according to all the scales in all the cases turned out to be highly significant from viewpoint of statistics ($p < 0,0005$).

In control group (Table 6, Fig. 2) original PH integral point made up $45,6 \pm 1,5$, while the lowest index was the one according to pain intensity scale (BP) – $22,9 \pm 3,5$, the highest one – according to physical functioning scale (PF) – $46,0 \pm 4,1$.

Table 1. Criteria for inclusion in and exclusion out of the research

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Pain syndrome lasting over 6 months; • Active complaints before and at the moment of research start; • Male sex; • Age over 30, under 60; • Diagnosis of lumbodinia/ lumbar ischialgia or local myofascial pain established by a neurologist; • Accomplishment of instrumental visualizing examination (computed tomography/magnetic resonance imaging) of lumbar spine and sacral spine 	<ul style="list-style-type: none"> • Clinically significant symptoms of neurologic impairment which are active at the moment of treatment start; • Destructive processes and/or apparent osteoporosis of vertebral bodies (according to visualization evidence); • Evident constrictive process in a vertebral canal (according to visualization evidence); • Suspected vascular (ischemic) genesis of the disease; • Neurosurgical operations on the vertebral column in the past history; • Severe associated diseases: high degree of arterial hypertension, coronary heart disease, cardiac malformations, cerebrovascular disease, cardiovascular collapse, respiratory or renal failure, noncompensated diabetes mellitus, rheumatologic diseases in active phase (including febrile states of nonspecified origin), chronic infectious diseases, mental diseases (incl. those in the past history), malignant neoplasms (incl. those in the past history) or assumption of them

Table 2. Members and characteristics of index group and control group

Parameters of the groups	Index group	Control group	Total
Number of patients (n) at the beginning of the research	15	15	30
Number of patients (n) at the end of the research	15	15	30
% of patients who have passed through the research till the end	100%	100%	100%
Average age of the patients, years	45,5±1,7	43,1±1,3	44,0±1,1
Minimal age of the patients, years	35	35	35
Maximal age of the patients, years	55	53	55

After treatment PH integral point made up 48,2±1,4, i.e. it grew by 2,7±0,7. The biggest progress was registered in this group according to pain intensity scale (BP) – by 34,5±2,8.

6 months after treatment completion average PH integral point equalled to 46,0±1,2, i.e. it almost got back to its original value (the difference of 0,5±1,0). Analysis of the dynamics according to different scales showed that there was kept a moderately marked positive difference from the original level according to role functioning scale (RP) – 15,0± 5,9, and according to pain intensity scale (BP) the point was still higher than the original one, too – by 13,9± 2,7. According to PF scale average point turned out to be even lower than the original one.

Table 3. Act of examination of the research participants

No	Research method	Comment
1.	Collecting complaints and anamnesis	Checkup, incl. testing according to inclusion/exclusion criteria
2.	Neurologic examination	Accomplished by neurologist, with the record of the diagnosis established
3.	Visualizing instrumental examination of sacro-lumbar spine (computed tomography/magnetic resonance imaging)	Checkup, incl. testing according to inclusion/exclusion criteria. The results of the earlier examination (no older than 1 year) were taken into consideration.
4.	SF-36 health survey	Methods of the survey results processing and scale indices calculations are given in Appendix 1.3, while the results of primary processing of index group survey results – in Appendix 2.1 and control group survey results – in Appendix 2.2.

Table 4. Indexes under analysis (within the groups)

Average values of SF-36 health survey scale indexes			
Indexes of separate scales of physical health (PF, RP, BP, GH) and integral indicator of physical health (PH).	Before treatment (0)	After treatment (1)	Six months after the treatment completion (2)
Indexes of separate scales of mental health (VT, SF, RE, MH) and integral indicator of mental health (MH).			

Table 5. The dynamics of results within the limits of SF-36 health survey testing in the index group (quality-of-life physical element)

indexes	Physical health				
	PF	RP	BP	GH	PH
original (0)	44,7±4,4	25,0±7,7	18,6±4,0	35,0±4,1	43,8±1,4
After treatment (1)	65,7±4,7	80,0±5,6	73,5±3,9	59,9±3,2	51,5±1,4
6 months later (2)	57,3±3,7	70,0±5,0	68,4±3,3	55,6±3,0	49,6±1,2
Δ(1-0)	21,0±4,0	55,0±8,9	54,9±4,2	24,9±3,0	7,7±1,5
Δ(2-0)	12,7±3,2	45,0±9,2	49,8±3,9	20,6±2,6	5,8±1,2

The differences according to all the scales in all the cases in this group proved to be highly significant from viewpoint of statistics ($p < 0,0005$).

The dynamics of quality-of-life physical element indexes in control group is shown in Fig. 2. Average indexes according to majority of scales after six months tend to get back to the values close to the original ones (measuring 0).

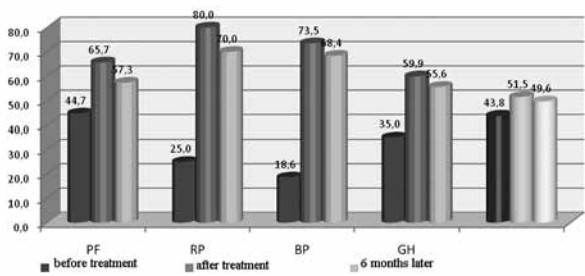


Fig. 1. The dynamics of SF-36 physical health indexes. Index group

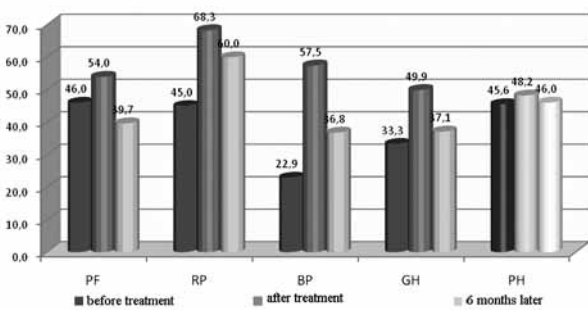


Fig. 2. The dynamics of physical health indexes according to SF-36 health survey. Control group

Table 6. The dynamics of results within the limits of SF-36 health survey testing in the control group (quality-of-life physical element)

indexes	Physical health				
	PF	RP	BP	GH	PH
Original (0)	46,0±4,1	45,0±7,4	22,9±3,5	33,3±4,2	45,6±1,5
After treatment (1)	54,0±4,2	68,3±6,7	57,5±3,9	49,9±3,9	48,2±1,4
6 months later (2)	39,7±3,2	60,0±5,3	36,8±2,9	37,1±3,5	46,0±1,2
Δ(1-0)	8,0±1,9	23,3±3,8	34,5±2,8	16,6±2,0	2,7±0,7
Δ(2-0)	-6,3±1,8	15,0±5,9	13,9±2,7	3,8±2,2	0,5±1,0

Table 7. The dynamics of results within the limits of SF-36 health survey testing in the index group (quality-of-life mental element)

indexes	Mental health				
	VT	SF	RE	MH	MH
original (0)	26,7±3,0	24,2±4,5	13,3±4,4	30,4±3,1	26,8±1,8
after treatment (1)	53,7±4,0	55,8±4,5	66,7±5,6	52,3±2,6	39,9±1,6
6 months later (2)	52,7±2,9	50,8±3,1	57,8±5,1	49,3±2,8	38,7±1,4
Δ(1-0)	27,0±3,0	31,7±5,4	53,3±6,3	21,9±2,1	13,2±1,3
Δ(2-0)	26,0±2,8	26,7±5,0	44,4±6,2	18,9±2,4	12,0±1,2

Quality-of-life mental element

Integral point according to the scales of quality-of-life mental element (MH) in the index group (Table 7, Fig. 3) originally equaled to 26,8±1,8, while the lowest point was the one according to role emotional functioning scale (RE) – 13,3±4,4, and the highest one – according to mental health assessment scale (MH) – 30,4±3,1.

After treatment completion MH integral point made up 39,9±1,6, i.e. it grew by 13,2±1,3. The most significant improvement was registered according to role emotional functioning scale (RE) which point was originally the lowest one and after treatment went up by 53,3±6,3.

6 months after treatment completion average MH integral point in the group made up 38,9±1,4, i.e. it was still higher than the original one by 12,0±1,2. The biggest difference was again according to role emotional functioning scale (RE) – 44,4±6,2 higher than the original one. Fig. 3 shows that 6 months after treatment completion average indexes according to all the quality-of-life mental health scales got just a little bit lower in comparison to the moment of treatment completion (measuring 1) and stayed much higher than the original ones (measuring 0). The differences according to all the scales proved to be highly significant from viewpoint of statistics ($p<0,0005$).

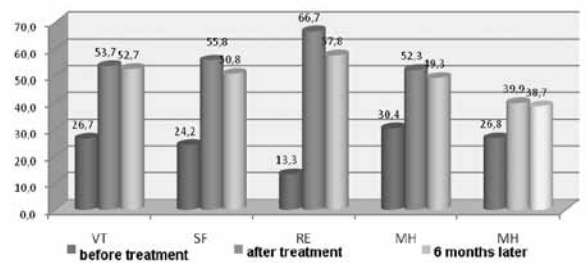


Fig. 3. The dynamics of mental health indexes in index group (according to SF-36 survey)

General regularities in quality-of-life indexes dynamics within the groups

In both groups statistically significant improvement of quality-of-life index was registered as a result of the treatment. From viewpoint of physical health, the biggest progress was registered according to pain intensity scale, which original point was the lowest one. From viewpoint of mental health, the most considerable progress was the one according to emotional role functioning scale (RE), which original point was the lowest, too.

The second testing conducted 6 months after the treatment completion showed that the statistically significant difference between the current index

Table 8. The dynamics of results within the limits of SF-36 health survey testing in control group (quality-of-life mental element)

Indexes	Mental health				
	VT	SF	RE	MH	MH
original (0)	34,3±1,7	31,7±2,4	17,8±5,5	38,1±1,9	30,2±1,3
After treatment (1)	60,0±1,8	57,5±4,5	44,4±7,0	53,3±1,8	40,6±1,2
6 months later (2)	42,0±1,4	41,7±2,6	26,7±5,8	43,5±1,3	34,3±1,3
$\Delta(1-0)$	25,7±1,8	25,8±4,1	26,7±4,8	15,2±1,8	10,4±0,8
$\Delta(2-0)$	7,7±1,8	10,0±2,5	8,9±6,1	5,3±2,0	4,2±1,0

values according to most of the scales and the original ones was still there in both groups. However, while in index group they decreased a little bit in relation to measuring 1 (immediately after treatment completion) and stayed considerably higher than the original ones (measuring 0), in control group there was a reverse regularity – index values according to most of the scales went down to a considerable extent and tended to approach to the original values.

In control group (Table 8, Fig. 4) original average MH integral point made up 30,2±1,3, the lowest index was the one according to RE scale – 17,8±5,5, the highest one – according to mental health assessment scale (MH) – 38,1±1,9.

After treatment completion average MH integral point equaled to 40,6±1,2, i.e. it grew by 10,4±0,8. The most significant progress was registered in the group according to RE scale – by 26,7±4,8, according to SF scale – by 25,8±4,1 and according to VT scale – by 25,7±1,8.

6 months after treatment completion average MH integral point equaled to 34,3±1,3, i.e. it was still higher than the original one by 4,2±1,0. The most marked progress was registered according to social functioning scale (SF) – by 10,0±2,5.

The differences according to all the scales proved to be highly significant from viewpoint of statistics ($p<0,0005$).

The dynamics of quality-of-life psychological element indexes in control group is shown in Fig. 4.

CONCLUSIONS

1. Osteopathic treatment of the patients with pain syndrome in lumbus and lower extremities leads to improvement of quality-of-life indexes from both physical and psychological viewpoints. The most significant shift was registered according to pain intensity scale and role emotional functioning scale, both of which originally had the lowest points and, consequently, reflected the parameters which dissatisfied the patients most of all.

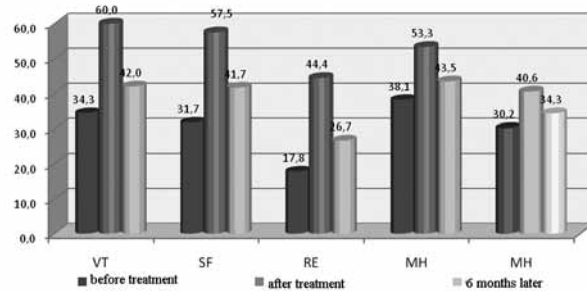


Fig. 4. The dynamics of SF-36 mental health indexes. Control group

2. The above mentioned improvement of QL indexes proved to be stable in the course of time.
3. The patients who received osteopathic treatment enjoyed significantly more considerable improvement of QL indexes according to all the SF-36 health survey scales in comparison to the patients who were treated with traditional methods. The difference was especially marked according to physical health scales.

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INTRAOPERATIVE APPLICATION EXPERIENCE OF VIIA RECOMBINANT HUMAN FACTOR IN PATIENTS WITH ITP AND COMPLICATED SUBDURAL HEMATOMA

M.I. Yeghiazaryan, L.A. Museyan, R.V. Fanardjyan, T.N. Khachatryan, M.V. Jilavyan

University Clinical Hospital "Heratsi", Yerevan, Armenia

Idiopathic thrombocytopenic purpura is known as the primary immune or autoimmune thrombocytopenic purpura represents the isolated immunomediated thrombocytopenia [11, 18] on the background of marrow normal function [20].

The disease is often revealed in women (72%) and in children until 10 years (40%) [20].

Numerous clinical researches have been shown that the reason of the ITP development is the disintegration of thrombocytes as a result of their phagocytosis antithrombocyte antibodies [11]. In the given process T-lymphocytes take immediate part ($CD4^+$) [8, 27], having the right cytotoxic influence on thrombocytes [24]. Besides, the patients with ITP $CD3^+$ lymphocytes can change the genes expression connected with apoptosis. In the result of $CD3^+$ lymphocytes can get fastness to corticosteroid therapy [23].

This classical theory, explaining ITP pathophysiology (antibodies synthesis against glycoproteids of a cytoplasmic membrane of thrombocytes-GPIIb-IIIa, GPIb-IX и GPIa-Iia – with their subsequent recognition Fc γ -thrombocytic receptors of macrophages and phagocytes) is considered old one nowadays [16, 18].

It is proved that disease can develop in 10–20% of cases in spite of antibodies formation process. According to other concept, the synthesis of the deformed thrombocytes by megacaryocytes and-or blockade of thrombocytes production provoke antithrombocytic antibodies [19].

In the ITP pathogenesis a special significance has the cytokines liberation disturbance, shown by activation Th0/Th1 of cells. As a result concentration IL-2 and IFN-g increases, but level IL-10 goes down, up to a total disappearance [6, 21].

The great interest represents the research of clinical role $CD8^+$ reactive cytotoxic cells concerning the thrombocytes which existence has been proved lately [19].

At ITP exacerbation, the clinical picture of the disease is expressed by dermal petechiasis eruption, cyanosis of mucosas in a kind of purpura, hypodermic

hematomas, nasal bleedings, and plentiful menstruations [18]. From all possible complications intracranial and subarachnoidal hemorrhages are most life-threatening [20].

Due to the ITP diagnostics, a particular interest represents the thrombocytopenia picture (thrombocytes $<100 \times 10^9/l$) [11] in the absence of a massive bleeding or an immune hemolysis on the background of normal indicators of a hemogram [14].

Nowadays 3 basic approaches of the ITP treatment are known [14, 22, 29]. However, in complications and massive hemorrhage, besides the basic treatment, the acceptance of emergency measures according to the references of the American society of hematologists [5], which consist in the appointment of high glucocorticoids, intravenous usage of immunoglobulin and platelet concentrate transfusion are necessary. The mechanism of glucocorticoids action in ITP isn't definitively found out; however there are the data confirming their influence on the reduction of synthesis of antithrombocytic antibodies, the depression of thrombocytes integration and wall capillaries strengthening [10].

The positive result by immunoglobulin treatment is caused by temporary suppression of reticuloendothelial system function, so-called "blockade of macrophages" [2, 17]. In the modern literature there is a disputable question on the transfusion necessity of a platelet concentrate. Undoubtedly, in the case of massive hemorrhage, the given tactics provides short-term haemostatic effect. According to a series of authors [12, 15, 28], in patients with ITP, a massive bleeding at concentration of thrombocytes $<20 \times 10^9/l$ doesn't form the basis for carrying out a specific therapy without fail since it can lead to deterioration of the basic pathology [25]. In such cases it is offered to prescribe NovoSeven – recombinant human factor VIIa (NovoSeven, Novonordisk, Denmark) [7, 9, 13, 26, 31] which is a preparation of a choice for urgent patients with a bleeding [30]. The mechanism of preparation efficacy consists in the connection of recombinant

human factor VIIa with the liberated tissue factor. The given complex activates factors IX, IXa, X and Xa. As a result there is a primary transformation of insignificant quantity of a prothrombin into thrombin which activates thrombocytes in the damage zone, factors V and VIII and, transforming a fibrinogen in fibrin, providing the formation of a haemostatic stopper.

To assume efficiency of this factor at disorder of a coagulative hemostasis, the patients with hemophilia have been allowed to apply the given preparation. The therapy of the Novo Seven preparation doesn't demand laboratory control. Lately, this preparation has been successfully used for treatment of bleeding which has no connections with hemophilia, namely in patients with liver function disturbances, at liver transplantation, and also for treatment of bleeding caused by an operative intervention and trauma [1]. There are data on high hemostatic efficiency of the Novo Seven preparation in the complex infusionally-transfusion therapy of a massive postnatal bleeding that testifies the expediency of its application of massive bleeding at obstetrics in childbirth-women with hemostasis pathology [3]. The preparation application in childbirth-women with ITP has allowed to refuse from the uteri extirpation and to keep reproductive function of women [4]. In the literature there is data about sufficient efficiency of the Novo Sevena appointment at subarachnoidal and parenchymatous hemorrhages [30].

We offer the results of the private experience on intraoperative applications of recombinant human factor VIIa in patients with ITP and complicated subdural hematoma.

The woman of 65 years was admitted with the complaints of headache, diplopia, the general delicacy and fatigability. According to her opinion the patient is ill within 15 days. Due to the anamnesis, the patient was administered prednizalon (120 mg/per day), strumectomy (eutiroxin, 5 mg/per day). The treatment was interrupted the last month. On the basis of objective examination at the moment of admission: the consciousness – clear, arterial pressure – 110/70 mm Hg, pulse – 100/minute, breath – independent, the frequency of respiratory movements – 14/minute. With the help of auscultation the lungs were defined vesicular breath, the lien wasn't palpated, the liver was located under a costal arch. In the neurologic status positive meningeal symptoms, disturbance of functions oculomotor and abducting nerves at the left, moderated tetra paresis with positive Babinsky symptom and increasing tendinous reflexes were revealed.

While carrying out MRI (fig. 1) and CT (fig. 2) of the brain it was revealed a number of bilateral, convexital, chronic, subdural hematomas with signs of

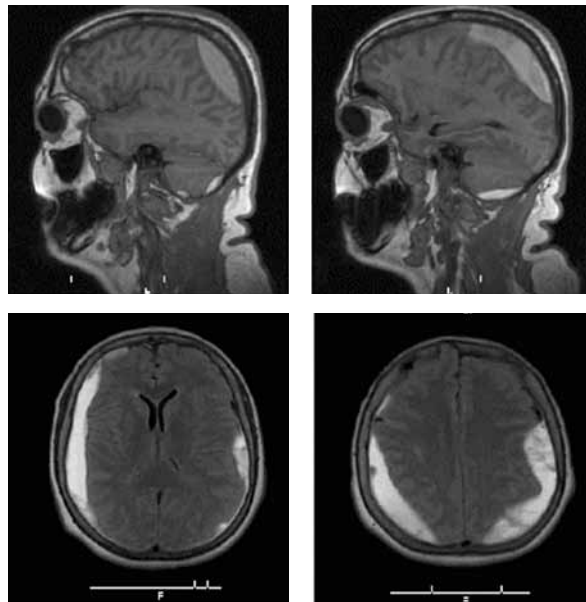


Fig. 1. MRI of the brain before the operation

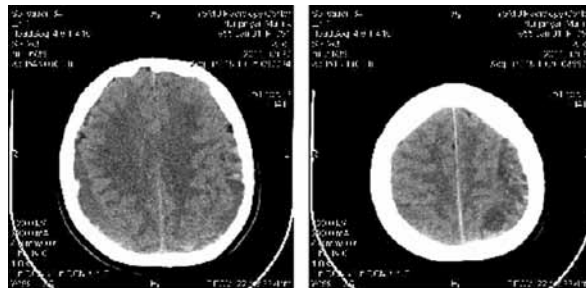


Fig. 2. CT of the brain before the operation

fresh repeated hemorrhage, as well as bilateral chronic subdural hematomas in the field of hemispheres of a cerebellum and mosto-cerebellum angle at the left.

The results of laboratory blood analyses were in norm limits, except for the concentration of thrombocytes which made up of $5 \times 10^9/l$.

Neurosurgeons came to the conclusion about the necessity of carrying out an operative intervention for the purpose of bilateral subdural hematomas ectomia through dilated cutter apertures.

The preparation for surgery included the prednizalon therapy (120 mg/per day) in the result on the third day there was the increasing thrombocytes level of blood up to $26 \times 10^9/l$ that had the basis for an urgent operation.

Before the anesthetic induction of the patient, the analog of the Novo Sevena preparation – the Eptakog-alpha (4.8 mg) was applied. Anesthesia proceeded without complications. The hemorrhage made up less than 500 ml that was the basis for the refusal of blood

transfusion preparations. In the intraoperative period it was not observed complications in the form of the lowered blood coagulability and bleeding. After the operation the patient was exuberated and transmitted into the intensive care ward. The postoperative period proceeded without complications. Within ten days the level of thrombocytes increased up to $255 \times 10^9/l$. Wounds became healthy by the first intention, progressive disappearance of complaints and disturbances of neurologic character (fig. 3) were perceptible. The patient was discharged from the hospital in a satisfactory condition.

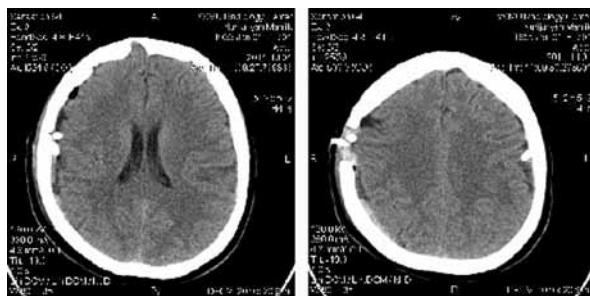


Fig. 3. CT of the brain after the operation

Thus, our experience of Eptakog alpha application in the patient with ITP has shown that the preparation is capable to warn bleeding development in the intraoperative period.

The Introduction of modern haemostatic preparations in complex therapy of the ITP complications will allow minimizing the volumes of donor blood components, to reduce the frequency of serious post-operative hemotransfusionic complications.

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ANALYSIS OF CONCEPTS OF PSYCHOANALYTIC PSYCHOSOMATICS

E.P. Filimonova

*Scientific Research Institute of Kuban State University of Sport, Culture
And Tourism, Krasnodar, Russia*

Today the meanings “psychosomatics” and “psychosomatic medicine” are associated with numerous research directions that are not homogenous and not coordinated with each other in selection of approaches and methods of researches. The modern psychosomatic medicine developed dramatically in the latest fifty years is not conceivable without psychoanalysis. It owes psychoanalysis the stimulus for systematical study of psychosomatic interrelations in the disease process, a number of fundamental conceptions for theory and practice, which still remain the postulate and the ground of psychosomatics. At the same time the attitude of psychoanalysis towards the problem of psychosomatic diseases is not certain; quoting Freud «it is an uninvestigated borderline realm».

ACTUALITY. The available literature on psychoanalytical psychosomatics does not provide summarized systematized investigations of theoretical conceptions of psychoanalytical psychosomatics. Therefore, the absence of systematical investigations in this field and importance of the problem for psychoanalytical psychotherapy determined the theme of the present work.

INNOVATION OF THE RESEARCH. The present work is a first attempt so far to summarize rather few publications of domestic and foreign authors on psychosomatics.

OBJECT OF THE RESEARCH is a complex of theoretical aspects of psychoanalytical psychosomatics.

The aim of the research is assessment of different psychoanalytical conceptions of psychoanalytical psychosomatics.

THE FOLLOWING TASKS WERE PUT FORWARD:

- To trace down the main directions and approaches of domestic and foreign authors to the problem of psychosomatics and to compare them on the basis of historical consideration;
- To revise psychoanalytic theories of psychosomatics by S. Freud;
- To revise psychosomatic theories and models of S. Freud's early followers;
- To investigate modern conceptions of psychoanalytical psychosomatics.



senior research associate
info@newecology.ru

Methodological postulates of the work are theories and conceptions of leading psychoanalysts: S. Freud, F. Alexander, G. Ammon, O. Kernberg, H.J. Freyberger and others; and also leading foreign and domestic psychiatrists: V. Broitigam, P. Kristian, M. Rad, B. Luban-Plozza, V. Pöldinger, F. Krieger, K. Pederak-Hoffman, V. Podkorytov, A. Smulevich, V. Gindikin, Ya. Obuhov and others. Methods of the research are theoretical study, comparison, systematization of classical and modern psychoanalytical and medical literature.

PRACTICAL SIGNIFICANCE OF THE WORK.

The research deals with practical tasks on improvement of understanding of psychological mechanisms of psychosomatic disorders, which enables obtaining new connections and meaning in the psychoanalytic interaction, as well as reaching a new conclusion – that psychosomatics came to existence a century ago but has always been a practical instrument for genuine doctors. And today it has the right to become a fundamental science dealing complexly with etiopathic processes, which occur in the patient and hence the treatment should be multifaceted, with consideration of pathogenesis and aetiology of the disease and individual peculiarities of the patient. This approach for assessment and analysis of analytic conceptions and modern theories enabled to come to an important statement that psychosomatic diseases are determined by a fixation in the pre-oedipal stage of development with predomination of borderline level of the development of the psyche. The understanding of patient's psyche level is crucial for the choice of the technique for psychoanalytic psychotherapy.

NEW WAY OF CONSERVATIVE TREATMENT OF HERNIAS LUMBAR INTERVERTEBRAL DISKS

A.A. Oleynikov, A.G. Remnev

Vertebroneurology Centre, Sanatorium "Barnaulskiy", Barnaul, Russia

We have developed a new effective way of conservative treatment of hernias lumbar intervertebral disks (the patent for invention RU 2368401). The way complex also includes medicamentous blockade of painful points and electric stimulation a pulse electric current. Blockade of painful points was carried out in the field of lumbar vertebrae of a corresponding segment with hernia presence a intervertebral disk. An arrangement of electrodes for electric stimulation: the anode – a blockade venue (paravertebral), the cathode – a superficial electrode on a back surface of a shin. Characteristics of an electric current for stimulation: a current pulse, frequency of 50 Hz, a current strength 10–15 mA, duration of an electric impulse 0,2 ms. Duration of procedure of 8–10 minutes daily, on course of treatment of 10–12 procedures. Throughout four years by means of this way 372 patients with hernias lumbar intervertebral disks at the age from 22 till 59 years have been treated. At the reference to all patients detailed clinical research (MRI or CT), ultrasonic research of lumbar department of a backbone about revealing of hernias lumbar intervertebral disks was carried out. In a clinical picture at patients the painful syndrome of various degree of expressiveness, and also impellent and sensitive frustration at level of the bottom extremities prevailed. As a result of the spent treatment at the majority sick (321 – 86,3%) has been



Andrey A. Oleynikov
MD, PhD, Head of Altai
Vertebroneurology Center
aaolev@mail.ru

reached proof expressed (confirmed at the further dynamic researches) positive result. At 31 (8,3%) patients expressiveness of a positive effect was less, or the effect of treatment proceeded smaller quantity of time and it was required to spend additional courses of treatment. 20 sick (5,4%) subjectively didn't mark improvement while results of control researches testified to reduction of expressiveness hernia of intervertebral disk. Application of a new way of conservative treatment of hernias lumbar intravertebral disks hasn't revealed cases of deterioration of a condition sick, both clinical, and morfo-functional.

Thus, use of a new way allows to provide treatment of patients with hernias lumbar intervertebral disks. Result of this treatment is elimination of a painful syndrome, reduction of volume of a hernia of a disk, restoration radix conductivity. The new way of ultrasonic diagnostics of hernias lumbar intervertebral disks, developed by us, allows to provide objective diagnostics of hernias lumbar intervertebral disks, to establish exact localization of pathological process.

NEW WAY OF KNEE OSTEOARTROSIS TREATMENT

A.G. Remnev, A.A. Oleynikov

Vertebroneurology Centre, Sanatorium "Barnaulskiy", Barnaul, Russia

The knee joint of the person is under constant loading, keeps weight of a body of the person and provides great volume of movements of a foot. Constant loading on a knee joint leads to frequent enough development osteoarthritis. Knee osteoarthritis is in the lead is in the lead on frequency of occurrence of disease among articulate artrosis. At knee osteoarthritis there are degenerate-dystrophic changes in the hyaline cartilage covering condyles femoral and tibial of bones, in meniscuses, first of all. There are various ways of knee



Andrey G. Remnev
MD, PhD, Professor, Head
of Diagnostic Department,
Sanatorium Barnaulskiy
remnev@mail.ru

osteoarthritis treatment. On the basis of sanatorium "Barnaulskiy" we managed to develop the updating of a way of knee osteoarthritis treatment. At performance of this way of 50 Hz, a current strength till 7–10 mA, duration of an electric impulse 0,3 ms and medicinal

interstitial therapy electrophoresis a preparation Karpain, duration of procedure of 12–15 minutes daily, on course of treatment of 12–15 procedures carry out hypodermic introduction ozone-oxygen mixes and the subsequent electric stimulation of a place of introduction ozone-oxygen mixes an electric current frequency.

Application of this method leads to reduction and knocking over of a painful syndrome at patients with knee osteoarthritis, to reduction of inflammatory reaction of structures of a knee joint, restoration of function of a knee joint. 397 patients have been treated. The steady clinical effect of application of this way, received at treatment of patients with knee osteoarthritis joint allows to recommend this method for wide clinical application.

The complex diagnostic approach including radiological and ultrasonic researches is actively

applied to an estimation of presence and expressiveness of a pathology at level of a knee joint in sanatorium. In some cases, for specification of character of pathological process directed patients for research to treatment-and-prophylactic medical institutions of Barnaul for carrying out of a computer tomography or a magnetic resonance imaging of a knee joint. The method of ultrasonic diagnostics of a pathology of a knee joint is actively applied to control of results of treatment.

Thus, use of a complex method of knee osteoarthritis treatment allows to provide treatment of patients with knee osteoarthritis. Result of this treatment is reduction and knocking over of a painful syndrome at patients with knee osteoarthritis, reduction of inflammatory reaction of structures of a knee joint, restoration of function of a knee joint.

ZEHN-JAHRE EXTRAKORPORALE STOSSWELLENTHERAPIE (ESWT) BEI PSEUDARTHROSEN

Frank Bätje¹, Helmut Lilp², Jürgen Kopp³

¹Praxis für Extrakorporale Stosswellentherapie (ESWT), Hannover

²Klinik für Unfall- und Wiederherstellungschirurgie

³Klinik für Plastische und Handchirurgie Diakoniekrankenhaus Friederikenstift, Hannover

EINLEITUNG: Unverheilte Knochenfrakturen werden nach drei Monaten als verzögerte Knochenbruchheilungen und nach sechs Monaten als Pseudarthrosen bezeichnet. Im durchschnittlichen Patientengut in Staaten mit gut organisiertem Trauma-management resultieren diese Knochenheilungsstörungen in Häufigkeiten von z.B. 4,5% an der Klavikula, 4,3% nach Tibiaumstellungsosteotomien oder allgemein max. 7%. Operative Korrekturingriffe gelten als Therapiegoldstandard spätestens im Pseudarthrose-Stadium. In ausgewählten Fällen führen wir auch nicht-invasive Extrakorporale Stosswellentherapien durch und erwarten dadurch Knochenstoffwechselstimulationen, die denen operativer Eingriffe ähnlich sind.

MATERIAL UND METHODEN: Seit 2001 haben wir mehr als 450 ausgesuchte Knochenheilungsstörungen frühestens drei Monate posttraumatisch bzw. nach letzter Osteosynthese mittels fokussierter hochenergetischer Stosswellentherapie mit oder ohne computerassistierte Navigation ambulant behandelt. Überwiegend jene Patienten, die Arbeitsunfallopfer waren, wurden fachunfallchirurgisch nachuntersucht oder mittels Fragebogen kontrolliert.



Dr. med. Frank Bätje
Lavesstraße 6, 30159 Hannover
Tel. 0511 / 35399741
Fax 0511 / 35399742,
info@dr-baetje.de

ERGEBNISSE: Ausreichend stabile Frakturheilungen und weitere Therapieerfolgskriterien wurden unabhängig von der Art der primären Behandlung in 80% nach zwei bis sechs Monaten festgestellt. Delayed und non-unions, atrophe und hypertrophe Formen sowie Zustände nach einfachen oder Trümmerfrakturen, Osteotomien oder Arthrodesen kleiner und großer Knochen wurden zusammengefasst, weil sie dem üblichen Spektrum entsprechen.

SCHLUSSEFOLGERUNG: Die ESWT wird nur in einigen Staaten und dort auch nicht flächendeckend für die operationersetzende Frakturbehandlung eingesetzt. Unsere retrospektiven Fallkontrollen am eigenen Patientengut weisen auf ermutigende Therapieerfolge und gänzliche fehlende Komplikationen hin und liegen im Trend jener Studien höherer Evidenzgrade, die in den ESWT-Zentren in Österreich, Taiwan oder Kolumbien publiziert worden sind. In Deutschland wird die ESWT nur ausnahmsweise von institutionellen Kostenträgern bezahlt, obwohl die Gesamtkosten sehr deutlich geringer sind als für stationäre Operationen

in Narkose. Außerdem existieren geeignete Stosswellentherapiegeräte nur punktuell und spezialisierte

Ärzte noch seltener. In Hannover können alle in Frage kommenden Fälle zeitnah versorgt werden.

CHANGES OF RHEOLOGICAL INDICATORS OF ERYTHROCYTES IN ARTERIAL HYPERTENSION, COMPLICATED WITH MYOCARDIAL INFARCTION AND STENOCARDIA

A. Khama-Murad, N. Heydarian, K. Akhanchikova

I.P. Pavlov Physiology Institute, Saint Petersburg, Russia

I.P. Pavlov Saint-Petersburg State University, Saint Petersburg, Russia

A.S. Pushkin Leningrad State University, Saint Petersburg, Russia

It is shown that in the case of arterial hypertension, rheological properties of the main carriers of oxygen and metabolites in blood are disordered, though, in case of cerebral ischemic affections these changes are absent. With appearance of the newest methods of erythrocytes' plastic properties research there also appeared a possibility to specify our conceptions about an intensity degree of hemodynamic disorders in the case of vascular system diseases.

MATERIAL AND METHODS. In our research were 12 men, who suffered from an arterial hypertension, complicated with stenocardia, and 12 patients with myocardial infarction, 6 women and 6 men. A control group was 15 healthy patients of proper age, 12 men and 3 women. We have examined main rheological determinants of erythrocytes by straight adequate methods in whole blood. Deformability was examined by diffracting osmoscany method, aggregative properties – with the help of piezodynamic method in a microcuvette on installations. The methods used let us estimate not only integral indicators of erythrocytes' deformability and aggregation, but also assess sphericity (S/V ratio), internal viscosity of erythrocytes, aggregations' solidity and the speed of their spontaneous formation in whole equalized blood. The blood was taken from ulnar vein on an empty stomach in the morning into test tubes with heparin at 150 units/ml.

RESULTS OF RESEARCH. Deformability index was heightened in both groups of patients. An Omy indicator's decrease in both groups of patients is noticed: (159 ± 8) mOsm with arterial hypertension and myocardial infarction and (157 ± 9) mOsm – with stenocardia against (148 ± 7) mOsm in healthy people ($p < 0,05$). Subject to this proviso, a slight decrease of O' indicator is mentioned: (397 ± 9) mOsm and (393 ± 10) mOsm accordingly against (404 ± 12) mOsm in control. Regarding spontaneous aggregation, both minimal (an indicator Uo) and maximum (Oq) aggregates' solidities to mechanical destruction increase, which leads to reliable increase of aggregation index from $(1,2 \pm 0,4)$ rel. units in control to $(2,3 \pm 0,5)$ rel. units in the case of infarction ($p < 0,01$) and $(1,8 \pm 0,3)$ rel. units ($p < 0,05$) with stenocardia. Change of Omy indicator is less pronounced, but increase of deformability, in comparison with men, is more significant. Strength properties of erythrocytes' aggregations and the speed of their spontaneous formation are higher among women. So, the aggregation speed among women, who suffer from myocardial infarction, increases in 12%, while among men – only in 5%.

DISCUSSION. Our research have shown an absence of significant changes of erythrocytes' deformability among patients, who suffer from arterial hypertension with myocardial infarction and bouts of stenocardia, but, reliable change of erythrocytes' sideview with decrease of S/V ratio (change of Omy indicator) is mentioned, that is swelling of red cells, and also a tendency to dehydration of hemoglobin (O' indicator), that is decrease of internal viscosity of erythrocyte. Regarding sex differences in dynamics of disease, we can presuppose that correction of deformative properties of erythrocytes among women occurs in a more pronounced way, in comparison with men. Though, a risk of ischemic affections, due to a heightened aggregation status among women, is higher.

CHOICE OF METHOD OF SURGICAL TREATMENT IN CHILDREN WITH ECHINOCOCCOSIS LUNG

H.I. Ibodov, A.M. Sharipov, B.Dz. Azizov

Tajik Institute of Postgraduate Medical Training, Dushanbe, Tajikistan

OBJECTIVES OF THE STUDY. Improved results of surgical treatment of children with various forms of echinococcosis of the lungs.

MATERIALS AND METHODS. Over the last 10 years in the Department of Paediatric Surgery of the Tajik Institute of Postgraduate Medical Training were on the treatment of 152 patients with lung

echinococci. (EL) in various forms. Children aged 2–7 years were 52.8, 10 years – 33, 11–15 years – 67. Solitary echinococcal cyst 144 (94,7%). Bilateral lesion in 8 (5,3%) children. In 16 (10,5%) patients had pulmonary hydatid cyst combined with lesion of the liver. Right-sided localization (59), left-handed (41%). According to the location in tissue lung echinococcus more (126) and other central located, less (26) on the periphery.

Depending on the size and scope of the EC (in the classification of A.T. Pulatova) were small amount of 10–100 ml, diameter of the residual cavity of 4–7 cm (6), medium – 100–250 ml, diameter – 7–10 cm (24), large and huge volumes of 500 or more (71). Among the complicated forms of echinococcosis patients with a breakthrough in the bronchus was 42, in the pleural cavity – 4, a breakthrough in the bronchus and the pleural cavity – 2, suppuration of the residual cavity of the EC – 3, recystic inflammation – 15. In the diagnosis of the disease was mainly used radio logic method of investigation (152). In 106 observations for the diagnosis, the timing and extent of surgical intervention was used ultrasound (U.S.).

RESULTS AND DISCUSSION. We used two-stage disclosure of thoracic injuries in 71 patients with large and giant cyst of the lungs. It consisted of the following: first produced torakotsentez dissection of parietal pleura in the course of the wound for 5–10 cm Surgeon finger bluntly and gently detaches contiguous portion of the fibrous capsule, given that it was possible to separate the edge of 4–5 cm and thereby partially exposing cyst. Then sucked all the way to puncture echinococcus fluid, then dissected and removed fibrous capsule chitinous shell. Cavity of the fibrous

capsule is disinfected and loose plugging. Easy fully released from adhesions. In order to prevent recurrence of echinococcosis There are many ways is the use of 1–5% formalin solution. We have 20 (30,4%) patients in the control group was used 2% formalin solution. In this case, bronchospasm, we observed in 5 patients, cardiac arrhythmias (bradycardia) in 4 patients. In the clinic of pediatric surgery until 1996 when centrally located cyst easily applied method, developed by A.T. Pulatov in 1982 – is the creation of artificial interlobar or intersegmental grooves. In this procedure, operated on 56 out of 152 patients, including 13 with complications. In this case, 14% of the 56 patients had complications in the postoperative period in the form of education residual cavity in 2 patients and neparaziterial cyst in one patient. We have been modified to create an artificial interlobar or intersegmental grooves. In this method, operated on 90 children from 152 patients. Complicated by pulmonary EC were 38, the average EC in 16, large lung EC were 20, a giant 16. The technique is as follows: after the disclosure of the residual cavity formed in the hemisphere, further dissected fibrous capsule with minimal thin layer of lung tissue in the course of vessels and bronchi to the bottom within a functioning lung tissue to 2–3 cm excised edge of the fibrous capsule is imposed several eight-shaped, nonabsorbable hemo and aerostatic seams. formed three additional artificial interlobar or intersegmental fissure. When inflating the lung surface of all the fibrous capsule are closed, as the concave surface on the fibrous capsule is completely eliminated. Thus echinococectomy with various forms of lung EC children, our technique is more efficient surgical treatment, postoperative complications of this technique is 9% against 14.8% for traditional ones.