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BLOOD COAGULATION POTENTIAL IN PATIENTS WITH MYOCARDIAL INFARCTION AFTER THROMBOLYSIS AND POSSIBILITIES OF ITS CORRECTION USING MAGNETOTHERAPY

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The purpose of the study was to investigate the magnetotherapy efficacy aimed at blood coagulation potential and fibrinolytic activity improvement in patients with acute myocardial infarction with ST-segment elevation after thrombolysis at the inpatient stage of rehabilitation. 80 patients with acute myocardial infarction with ST-segment elevation were included in the clinical observation. These patients were randomized into 2 groups. Group 1 consisted of 40 patients treated using thrombolytics with adjuvant therapy and standard cardiovascular drugs. Group 2 consisted of 40 patients who were additionally prescribed the course of magnetotherapy. All patients' blood coagulation potential was analyzed, including the coagulative and anticoagulative chains and fibrinolytic activity standardized indexes. The data obtained showed that parameters of hemostasis quickly return to normal values in patients with acute myocardial infarction with ST-segment elevation 2–3 days after thrombolytic therapy and heparin administration that demonstrate combined moderate blood procoagulative system activation against the background of both anticoagulative and fibrinolytic systems reduced activity. The developed tendency to hypercoagulation duration is maintained throughout the entire inpatient period reaching maximum before the patients' discharge. The course of magnetotherapy in the complex treatment of patients with acute myocardial infarction with ST-segment elevation stimulates a favourable impact on hemostasis coagulative and anticoagulative systems imbalance toward its coagulative potential reduction and fibrinolytic activity increase. The authors suppose that the original magnetotherapy method is easy to perform, effective in blood hypercoagulative state reduction, does not induce side effects, and can be recommended to patients with acute myocardial infarction with ST-segment elevation of any age and weight category after thrombolytic therapy.

Key words: acute myocardial infarction, thrombolysis, magnetotherapy, blood coagulation, blood coagulative and anticoagulative systems, fibrinolysis.

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СТАН КОАГУЛЮЮЧОГО ПОТЕНЦІАЛУ КРОВІ У ХВОРИХ З ІНФАРКТОМ МІОКАРДА ПІСЛЯ ТРОМБОЛІЗИСУ ТА МОЖЛИВОСТІ ЙОГО КОРЕКЦІЇ ЗА ДОПОМОГОЮ МАГНІТОТЕРАПІЇ

Метою дослідження було вивчення ефективності магнітотерапії, спрямованої на покращення коагуляційного потенціалу крові та фібринолітичної активності у хворих на гострий інфаркт міокарда з підйомом сегмента ST після тромболізису на стаціонарному етапі реабілітації. Для клінічного спостереження були залучені 80 хворих на гострий інфаркт міокарда з підйомом сегмента ST. Ці пацієнти були рандомізовані на 2 групи. 1 групу склали 40 хворих, яким застосовували тромболітики з ад'ювантною терапією разом із стандартними серцево-судинними препаратами. 2 групу склали 40 хворих, яким додатково призначали курс магнітотерапії. У всіх пацієнтів аналізували коагуляційний потенціал крові, включаючи коагуляційний та антикоагуляційний ланцюги разом зі стандартними показниками фібринолітичної активності. Отримані дані довели, що у пацієнтів з гострим інфарктом міокарда з підйомом сегмента ST показники гемостазу швидко повертаються до нормальних значень через 2–3 дні після тромболітичної терапії та введення гепарину, що демонструє сумісну помірну активацію прокоагулянтної системи крові на тлі зниженої активності антикоагулянтної та фібринолітичної систем. Сформована схильність до гіперкоагуляції зберігається протягом усього стаціонарного періоду, сягаючи максимуму перед випискою хворих. Курс магнітотерапії в комплексному лікуванні хворих на гострий інфаркт міокарда з підйомом сегмента ST нормалізує дисбаланс зсідаючої та антизсідаючої систем гемостазу в бік зниження його коагуляційного потенціалу та підвищення фібринолітичної активності. Автори висловлюють, що оригінальний метод магнітотерапії є простим, ефективним у зниженні гіперкоагуляційного стану крові, не викликає побічних ефектів і може бути рекомендований для призначення хворим на гострий інфаркт міокарда з підйомом сегмента ST будь-якого віку та вагової категорії після тромболітичної терапії.

Ключові слова: гострий інфаркт міокарда, тромболізис, магнітотерапія, зсідання крові, системи зсідання та анти зсідання крові, фібриноліз.

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The total mortality from cardiovascular diseases has seen to be increased in Ukraine in the last decade, resulting in the population's average life duration shortening [2, 3]. Both ischemic heart disease and especially acute myocardial infarction (AMI) occurred to be the leading factors in this negative process [6]. Approximately 35 % of patients die from it, with approximately the same number of patients – at the pre-hospital stage [2]. Another 15–20 % of patients who survived throughout the acute stage die within the first year after [5]. The risk in post-infarction patients' mortality significantly increased also – even 10 years after is 3.5 times higher pertaining to the analogous healthy individual's data [5]. Therefore, the problem of this contingent of patients' optimal treatment searches remains extremely relevant.

The first results reflected mortality reduction in patients with AMI with ST-segment elevation was achieved due to thrombolytic therapy (TLT) advances, which was actively used abroad since the early 1990s [12] and in Ukraine with a 10-year delay [4]. An additional method came into practice in the 2010s that reduced mortality: percutaneous coronary intervention (stenting) – a minimally invasive procedure for infarction-related coronary artery recanalization [4].

These two methods are the determining factors in modern tactics for patients with AMI management [7]. Their comparative efficacy results show that both tactics are not mutually exclusive but even complement each other.

Recanalization during TLT is possible to increase with the help of so-called "early" thrombolysis (i.e., the pre-hospital stage in an ambulance) that permits the achievement of results comparable with both angioplasty and stenting [11]. The clinical studies were also conducted to improve the clash with rethrombosis, which resulted in adjuvant therapy efficacy enhancement starting from antiplatelet agents and unfractionated heparins use till double antiplatelet therapy and low-molecular-weight heparins use during 2–8 days [8].

However, it should be noted that reocclusion risk is relatively high not only during this first week of treatment; such risk was proved to occur 6–12 hrs after in 5–12 % of patients, 30 days after – in 10–25 %, and 3–6 months after – in 25–35 % of patients, i.e., during the period when the patient has not only completed the rehabilitation stage but also stays home [9]. Besides, the above-described adjuvant therapy scheme is recommended for patients before 75 years weighing above 60 kg due to the proven risk of "major" bleeding [10].

Hence, the search for methods of blood hypocoagulant potential prolongation in patients after thrombolytic therapy at the late inpatient and post-inpatient stages of rehabilitation continues to be relevant, especially for patients safety over 75 years and with low body weight together with patients with long-term anticoagulant therapy contraindications (risk of bleeding, especially gastrointestinal, intracranial and intraocular, the need for their combined use with non-steroidal drugs, liver insufficiency, allergic reactions, etc.).

Magnetotherapy (MT), from this point of view, is of particular interest due to its proven antianginal, hypocoagulant, hypotensive, antiradical, and microcirculation-improving effects [1, 14]. Vitally important that MT enhances the drug effect and keeps it throughout 3–6 months [1]. We supposed that clinical significance is that it is one of the safest preformed physical factors that might be used in patients of any age with any body weight at inpatient and outpatient rehabilitation stages.

The purpose of the study was to investigate the magnetotherapy efficacy aimed at blood coagulation potential and fibrinolytic activity improvement in patients with acute myocardial infarction with ST-segment elevation after thrombolysis at the inpatient stage of rehabilitation.

Materials and methods. 80 patients with AMI with ST-segment elevation were included in the clinical observation at the Cardiology department after thrombolytic therapy. We obtained written permission from each patient or their relatives to use these case histories.

These patients were randomized into 2 observation groups according to the therapy used. These two observation groups were statistically comparable using all anamnestic, parametric, clinical, and laboratory criteria.

Group 1 (control group) consisted of 40 patients who were treated using thrombolytics (alteplase or streptokinase according to generally accepted regimens) with a course of adjuvant therapy (aspirin and enoxaparin for 7 days or 5 days for people prone to bleeding and over 75 years old) together with standard cardiovascular drugs (nitrates, angiotensin-converting enzyme inhibitors, antiplatelet agents, beta-blockers, diuretics) to compensate and stabilize cardiac activity.

Group 2 (the group of observation) consisted of 40 patients who were additionally prescribed the course of MT according to our original method [14]. To enhance the hypocoagulant effect, the simultaneous magnetic influence was directed to two zones maximally filled by blood – the heart and liver areas. Two different types of magnetic fields – alternating (heart area, 20 mT) and sinusoidal (liver area, 14 mT) – were used simultaneously with a frequency equal to 50 Hz. Each MT course included 10 daily procedures with a single exposure of 20 min.

The mean duration of both the fractionated and unfractionated heparins course was equal to 7.57±0.32 days. The MT course of magnetic therapy started 2–3 days after the heparin finish and lasted an average of 12.68±3.42 days of myocardial infarction manifestation.

All patients' blood coagulation potential was analyzed, including the coagulative and anticoagulative chains and fibrinolytic activity standardized indexes. The international normalized ratio (INR) reflected the external coagulation mechanism activity, activated partial thromboplastin time (APTT)

outlined the internal coagulation mechanism functioning, and plasma tolerance to heparin reflected the anticoagulative chain.

Blood samples were collected from a peripheral vein 2–3 days after heparin therapy termination (8–10 days of disease) and once more before discharge from the hospital (25–30 days).

The results are presented as M±m, where M is the arithmetic mean and m is the standard error of the mean. The groups were tested for the Gaussian distribution using the Shapiro-Wilk test. Mann-Whitney U-test was calculated to measure the significance of differences in quantitative characteristics between groups' estimations. All the statistical calculations were done with the help of "Statistica 10.0" software. The minimal statistical probability was determined at $p<0.05$.

Results of the study and their discussion. Blood coagulation potential in patients with AMI was monitored 2–3 days after thrombolysis and heparin week-long course of therapy, corresponding to 8–10 days of the disease (Table 1).

Table 1

The indices of coagulation system in patients with acute myocardial infarction after thrombolytic therapy and heparin therapy termination and during the inpatient period

Indices of the coagulate system after thrombolytic therapy and heparin therapy termination		
Index	Normal value	Patients with AMI
International normalized ratio	1–1.4	1.92±0.04
Activated partial thromboplastin time, sec	30–35	31.55±1.02
Plasma tolerance to heparin, min	10–16	7.55±0.15*
Fibrinolytic activity, min	230–350	410.3±30.8*
Indices of coagulate system dynamics after thrombolytic and heparin therapy during the inpatient period		
Index	After TLT and heparin therapy	At the end of the stationary period
International normalized ratio	1.92±0.04	1.84±0.03
Activated partial thromboplastin time, sec	31.55±1.02	29.03±0.61#
Plasma tolerance to heparin, min	7.55±0.15	7.01±0.11#
Fibrinolytic activity, min	410.3±30.8	405.8±41.4

Note: * – $p<0.05$ – the significant differences of the investigated indexes vs the analogous normal values; # – $p<0.05$ – the significant differences of the investigated indexes vs the analogous data after TLT and heparin therapy (Mann-Whitney U-test).

It is evident that the most sensitive and WHO-recommended index of INR. However, it somewhat exceeded its normal values (1.9 vs 1.4) and was insufficient compared to those recommended for patients with AMI.

We suppose this indicates in favour of blood coagulation external mechanism rapid (on the 2^{nd}–3^{rd} days) return to normal values after TLT and heparin therapy. The same trend was supported by the blood coagulation internal mechanism index equal to 31.55±1.02 sec, which was practically at its lower normal limit.

We received data showing plasma tolerance to heparin increased due to its absolute value of 7.55±0.15 min, less than the normal value ($p<0.05$). Blood fibrinolytic activity was also increased ($p<0.05$).

We tried to follow the time duration of blood-formed hypercoagulable conditions in observed patients during the inpatient period. The mean treatment duration was equal to 28.6±3.5 days. That's why we analyzed the abovementioned indices change compared to the same data before patients are discharged from the hospital.

One could see that the INR index immediately after TLT and heparin therapy quickly returned almost to normal data and demonstrated a further tendency to decrease (1.84±0.03; $p>0.05$) during the inpatient period.

APTT index, which demonstrated a tendency to clots formation 2–3 days after the heparin therapy end (31.55±1.02), showed a greater increase in this risk till the end of the stationary period (29.03±0.61; $p<0.05$).

We also registered plasma tolerance to heparin decrease till 7.01±0.11 min ($p<0.05$).

Blood fibrinolytic system activity analysis showed fibrinolysis suppression after TLT and heparin therapy (410.3±30.8). The investigated index of fibrinolytic activity did not change both 2–3 days after TLT and heparin therapy stop (410.3±30.8) and at the end of the inpatient period (405.8±41.4; $p> 0.05$).

We were interested in analyzing the impact of the MT course on blood coagulation anticoagulative chains and fibrinolytic activity (Table 2).

Both INR and APTT indexes after the MT course (1.86±0.05 and 30.48±0.69, relatively) showed a tendency to hypocoagulation.

The blood anticoagulative chain showed that with its significant suppression before the MT course, there was a reliable change in its activation after the MT course. This is evidenced by plasma tolerance to heparin index increase till 7.22±0.13 min after treatment ($p<0.05$). One could also see the tendency towards fibrinolytic activity restoration after MT course – the euglobulin lysis time was equal to 380.6±25.4 min ($p>0.05$).

Table 2

Blood coagulation potential dynamics in patients with acute myocardial infarction after thrombolytic therapy and magnetotherapy during the inpatient period

Index	Before MT course	After MT course
International normalized ratio	1.78±0.05	1.86±0.05
Activated partial thromboplastin time, sec	28.95±0.71	30.48±0.69
Plasma tolerance to heparin, min	6.64±0.15	7.22±0.13*
Fibrinolytic activity, min	402.2±20.3	380.6±25.4

Note: * – $p<0.05$ – the significant differences of the investigated indexes vs the analogous data before MT course (Mann-Whitney U-test).

The data presented showed quite a quick normalization (at the end of the first – beginning of the second week) of both links of the dynamically changing functional blood coagulation system in patients with AMI with ST-segment elevation. This was expressed as blood clotting coagulative chain activation, blood anticoagulative system activity decreasing, and fibrinolysis moderate inhibition. We suppose it's important that such blood coagulation system changes persist throughout the inpatient period, increasing until the end of hospitalization (25–30 days of AMI manifestation).

Altogether, this indicates a tendency of the blood coagulation system toward hypercoagulation and outlines an increased risk of rethrombosis in patients with AMI with ST-segment elevation, which is a significant risk of sudden death. Consequently, we made attempts to prevent this risk of hypercoagulation by a simple, safe, and non-drug MT method for which hypocoagulative and stationary effects are indicated [1]. As a result, the additional MT use during AMI treatment in selected patients positively impacted hemostasis system functional activity, eliminating the risks of hypercoagulation and possible rethrombosis after patients' discharge from the clinic. This is the first important point in the discussion of the results obtained.

Overall, our data complement our previous results in which the combined use of magnetic therapy and ω-3 polyunsaturated fatty acids induced an antioxidant effect in the course of stable angina [14] and are in a certain correspondence with the results of studies that summarized the constant magnetic field effects and highlighted its ability to activate the anticoagulant system, to reduce intravascular mural clot formation and to reduce blood viscosity by interfering with enzymatic processes, electrical and magnetic properties of blood cells that participate in hemocoagulation [15].

The second aspect of the data obtained analysis is necessary to discuss the expression of the fundamental positive effect achieved by MT use. Somewhat less MT effect, as it might be seen, was registered in the case of its impact on the prothrombin link of hemostasis. At the same time, the INR index dynamic is interesting – its value in the control group of patients one week after the treatment no longer corresponded to control indexes. One could register this index with a clear tendency for deterioration by the end of inpatient treatment, and after the course of MT, this index changed towards hypocoagulation.

The changes in the internal blood coagulation mechanism index indicate a similar direction of MT efficacy. APTT index in control group patients reached its limit values until the end of the first week of treatment, which showed the risk of thrombus formation significantly decreased by the end of the inpatient period. This index in patients of the observation group initially demonstrated a significantly higher risk of thrombus formation compared to control observations, although it slightly but increased as the result of MT.

The MT impact on the plasma hemostasis inhibitory system was significantly greater. Comparative analysis showed that if this system activity was initially suppressed and significantly worsened during the stationary period in the control group of patients, the MT influence significantly increased the investigated index.

Analysis of MT impact on blood fibrinolytic system activity in AMI patients with ST-segment elevation also showed a tendency towards its normalization.

Thirdly, the mechanisms of realization of MT cardioprotective effects are interesting. Pressure in deep and subcutaneous veins, as well as in arteries decrease, was noted under the influence of alternating magnetic fields.

The tone of the vascular walls was reported to be increased, and changes in their elastic properties and bioelectric resistance occurred. The MT hypotensive impact is associated with the bradycardiac effect and due to a myocardium contractile function decrease that resulted in MT high efficacy in load to myocardium decrease in patients with coronary heart disease [13].

Significant are the cerebral vessel tone reduction, brain perfusion improvement, and increased brain resistance to hypoxia after the influence of the low-intensity magnetic field [1]. The magnetic field promotes capillary blood flow acceleration, the contractility of the vascular wall improvement, and capillary blood filling increase.

Alternating magnetic field likelihood has a systemic effect on the entire body, confirmed by globulins synthesis, the acceleration under its influence together with sodium, potassium, magnesium, and iron ions content improvement in the liver, heart, and muscles. Low-intensity magnetic fields stimulate tissue respiration, nucleic acid metabolism, and protein synthesis and promote lipid peroxidation. In addition to

hypocoagulative impact, one could observe the sedative, hypotensive, anti-inflammatory, antiedematous, analgesic, regenerative, and immunoreactive magnetic field effects on the body [13].

Consequently, we registered MT general hypocoagulative efficacy at the inpatient stage of patients with AMI and ST-segment elevation rehabilitation after TLT and heparin therapy. This effect was influenced to a lesser extent by the external coagulation mechanism and to a greater extent by the internal coagulation mechanism and fibrinolysis.

Thus, there is no doubt about the MT prospects as a complex treatment component of acute myocardial infarction in terms of rehabilitation, effective prevention, and prognosis for life improvement in these patients and patients with coronary pathology in general. It should be stressed that there are still unclear and controversial mechanisms of MT cardioprotective effects mechanisms of implementation, its optimal modes and approaches to exposure, and MT combination with other treatments and types of rehabilitation, which only increases the importance of this area of clinical observations.

Conclusions

1. Parameters of hemostasis quickly return to normal values in patients with acute myocardial infarction with ST-segment elevation 2–3 days after thrombolytic therapy and heparin administration that demonstrate combined moderate blood procoagulative system activation against the background of both anticoagulative and fibrinolytic systems reduced activity.

2. The developed tendency to hypercoagulation duration is maintained throughout the entire inpatient period reaching maximum before the patients are discharged.

3. A 10-day course of magnetic therapy in complex treatment of patients with acute myocardial infarction with ST-segment elevation prescribed 2–3 days after the heparin therapy stops stimulates a favourable impact on hemostasis coagulative and anticoagulative systems imbalance toward its coagulative potential to reduce and fibrinolytic activity increase.

4. The original MT method used (two zones simultaneous use – heart and liver, two types of magnetic fields – sinusoidal and alternating, two degrees of magnetic inductance – 20 mT and 14 mT) is easy to perform, effective in blood hypercoagulative state reduction, does not induce side effects and can be recommended to patients with acute myocardial infarction with ST-segment elevation of any ages and weight category after thrombolytic therapy. It can be used additionally in patients with bleeding in anamnesis, together with non-steroidal drugs, as well as at the inpatient and outpatient stages of rehabilitation.

5. The magnetic therapy use as a component of acute myocardial infarction complex treatment in terms of rehabilitation, effective prevention, and prognosis for life improvement in these patients and patients with coronary pathology is promising.

Prospects for further research include the creation and implementation into the cardiological practice of a manual for magnetic therapy use in patients with acute myocardial infarction with ST-segment elevation for therapeutic and preventive purposes.

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ROLE OF SMALL INTESTINAL BACTERIAL OVERGROWTH IN THE DYSLIPIDEMIA AND NONALCOHOLIC FATTY LIVER DISEASE PATHOGENESIS

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Nonalcoholic fatty liver disease is one of the most prevalent chronic liver conditions, often associated with dyslipidemia and metabolic syndrome. Small intestinal bacterial overgrowth is considered a key mechanism potentially contributing to the development of non-alcoholic fatty liver disease and dyslipidemia by affecting metabolic balance, lipid metabolism, and systemic inflammation. This study examined 342 patients with dyslipidemia, assessing the prevalence of small intestinal bacterial overgrowth and its impact on lipid metabolism parameters and inflammatory markers. A significantly higher frequency of small intestinal bacterial overgrowth was found in patients with lipid metabolism disorders (53.4 %) compared to the control group (36 %, $p \leq 0.05$) and among those with non-alcoholic fatty liver disease (52 %). Correlation analysis confirmed the association of small intestinal bacterial overgrowth with elevated triglyceride levels, alkaline phosphatase, and insulin resistance index. The findings underscore the significance of small intestinal bacterial overgrowth in the pathogenesis of non-alcoholic fatty liver disease and dyslipidemia, highlighting new opportunities for the diagnosis and treatment of these conditions.

Key words: nonalcoholic fatty liver disease, small intestinal bacterial overgrowth, dyslipidemia, steatosis, steatohepatitis.

Х.Б. Квіт

ВПЛИВ СИНДРОМУ НАДМІРНОГО БАКТЕРІАЛЬНОГО РОСТУ НА РОЗВИТОК ДИСЛІПІДЕМІЙ ТА НЕАЛКОГОЛЬНОЇ ЖИРОВОЇ ХВОРОБИ ПЕЧІНКИ

Неалкогольна жирова хвороба печінки є однією з найпоширеніших хронічних патологій печінки, часто асоціюється з дисліпідеміями та метаболічним синдромом. Синдром надмірного бактеріального росту в тонкому кишківнику розглядається як ключовий механізм, що потенційно сприяє розвитку неалкогольної жирової хвороби печінки та дисліпідемій, впливаючи на метаболічний баланс, ліпідний обмін і системне запалення. У дослідженні обстежено 342 пацієнти з дисліпідеміями, серед яких оцінено поширеність синдрому надмірного бактеріального росту в тонкому кишківнику та його вплив на показники ліпідного обміну і запальні маркери. Встановлено значно вищу частоту синдрому надмірного бактеріального росту у пацієнтів із порушеннями ліпідного обміну (53,4 %) порівняно з контрольною групою (36 %, $p \leq 0,05$), а також серед пацієнтів із неалкогольною жировою хворобою печінки (52 %). Кореляційний аналіз підтвердив зв'язок синдрому надмірного бактеріального росту із підвищенням рівня тригліцеридів, лужної фосфатази та індексу інсулінорезистентності. Результати підкреслюють значущість синдрому надмірного бактеріального росту у патогенезі неалкогольної жирової хвороби печінки та дисліпідемій, що відкриває нові перспективи для діагностики та терапії цих захворювань.

Ключові слова: неалкогольна жирова хвороба печінки, синдром надмірного бактерійного росту, дисліпідемія, стеатоз, стеатогепатит.

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Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver pathologies worldwide, and its prevalence continues to increase due to the obesity and metabolic syndrome epidemic [14]. One of the key pathogenic mechanisms in the development of NAFLD is lipid metabolism disorder and the development of insulin resistance, which leads to dyslipidemia, particularly elevated triglycerides and total cholesterol levels. Moreover, increasing attention is being paid to the role of gut microbiota in the development of metabolic diseases, including NAFLD [3, 8].