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RISK MANAGEMENT OF COMPLICATIONS OF SURGICAL TREATMENT OF COLORECTAL CANCER BY CORRECTION OF THE HEMOSTASIS SYSTEM

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In 72 patients with verified colorectal cancer (T₂₋₄N₀₋₂M₀₋₁), who were planned and performed surgical intervention in order to prevent complications, including thrombohemorrhagic complications, comorbid burden was studied according to the Charlson comorbidity index questionnaire and the results of study of hemostatic potential (low-frequency piezothromboelastography) after functional test with double local ischemia of the upper limb. The predicted relative risk of thrombohemorrhagic complications was high (relative risk $r_{\text{THC}}=3.2$; $p=0.017$). In the patients with III–IV stages of the disease, the results of low-frequency piezothromboelastography corresponded to the decompensated or depleted type of reaction of the hemostasis system ($r=0.59$; $p=0.036$). Depending on the disorders identified in the patients, the following were used: antiplatelet agents, direct anticoagulants, bioflavonoids, cofactors of the components of the coagulation system, antifibrinolytic drugs. The use of the developed prophylaxis regimens made it possible to reduce the incidence of postoperative complications, the total share of which was 8.4 %, including: pulmonary embolism occurred in 1.4 % of cases and hemorrhagic complications – in 2.8 %.

Keywords: prognosis, risk, complications, colorectal cancer, surgical treatment, low-frequency piezothromboelastography

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УПРАВЛІННЯ РИЗИКАМИ УСКЛАДНЕНЬ ХІРУРГІЧНОГО ЛІКУВАННЯ КОЛОРЕКТАЛЬНОГО РАКУ ШЛЯХОМ КОРЕКЦІЇ СИСТЕМИ ГЕМОСТАЗУ

У 72 хворих з верифікованим колоректальним раком (T₂₋₄N₀₋₂M₀₋₁), яким планувалося і було проведено хірургічне втручання, з метою профілактики тромбоеморагічних ускладнень, визначено коморбідну обтяженість за опитувальником Charlson і результатами дослідження гемостатичного потенціалу (низькочастотна п'єзотромбоеластографія) після функціональної проби з подвійною локальною ішемією верхньої кінцівки. У хворих з III–IV стадією захворювання прогнозований відносний ризик був високим (відносний ризик тромбоеморагічних ускладнень склав 3.2; $p=0.017$), а результати дослідження гемостатичного потенціалу відповідали декомпенсованому, або виснаженому типу реакції системи гемостазу ($r=0.59$; $p=0.036$). Залежно від виявлених порушень у хворих під час лікування використовували: антиагреганти, прями антикоагулянти, біофлавіноїди, кофактори компонентів системи згортання, антифібринолітичні препарати: у вигляді монотерапії та за комплексними схемами. Розроблені схеми профілактики дозволили зменшити частоту післяопераційних ускладнень, загальна питома вага яких склала 8.4 %: у 1.4 % випадків виникла тромбоемболія легеневої артерії і в 2.8 % – геморагічні ускладнення.

Ключові слова: прогноз, ризик, ускладнення, колоректальний рак, хірургічне лікування, низькочастотна п'єзотромбоеластографія

The study is a fragment of the research project "Improvement of methods of diagnosis, prevention, correction and treatment of disorders of hemostatic potential in patients with predictable transient hypo- and hypercoagulable states in the perioperative period and at the stage of intensive care", state registration No. 0118U007322.

The morbidity rate of colorectal cancer (CRC) is increasing annually in most countries of the world. In 2019, in Ukraine, its level was 19.6 ‰, the mortality rate was 10.7 ‰, in 52.5 % of cases CRC was diagnosed at stage III-IV [2]. According to WHO, CRC is one of the most common forms of tumor diseases, the mortality rate from which in the world reaches 800 thousand cases per year, and in the general structure of cancer mortality – 9.0 % [7].

Risk factors for the development of the disease: chronic inflammatory diseases of the colon, smoking, alcohol consumption, predominance of red meat in the diet, diabetes mellitus, increased body mass index (BMI), low physical activity [12].

The surgical method is the main type of radical treatment and final staging of CRC. At the same time, the high frequency of septic, venous thromboembolic complications (VTEC), hemorrhagic complications (HC), especially in the elderly, requires the development of prognostic approaches at the preoperative stage [3]. According to the authors, the incidence of VTEC in the postoperative period up to 7 days reaches 1.2 %, up to 90 days – 4.3 %, smokers over 60 years of age with an increased BMI are more at risk [6, 8]. In the CRC patients the risk factors for VTEC, which developed during surgical treatment in 4.0–7.8 % of cases, were studied, more often complications developed in women with a high degree of risk on the scale of the American Society of Anesthesiologists (ASA) [9, 11, 14].

The authors' study reports on the development of thrombohemorrhagic complications (TEC) during surgical treatment in patients with gastric cancer and colorectal cancer in 7.5 % of cases. Risk factors were: female sex, advanced age (≥ 75 years), severity of the condition, the presence of a central venous catheter and chemotherapy in the preoperative period [10]. To prevent complications in such patients, an optimal choice of anesthetic management is required, based on objective indicators of the presence of individual risks for the development of VTEC and HC [1, 13].

The purpose of the work was to determine the individual risks of developing general somatic and thrombohemorrhagic complications during the surgical treatment of patients with colorectal cancer and to develop effective schemes for their prevention.

Materials and methods. The study included 72 patients with CRC who were admitted to the hospital of the Center for Reconstructive and Restorative Medicine of the Odessa National Medical University in the period from January 2017 to December 2018 for surgical treatment. The inclusion criteria for the study were: verified CRC (T₂₋₄N₀₋₂M₀₋₁) in patients aged 18 to 85 years, planned surgical treatment, and written informed consent to participate in the study.

The exclusion criteria were: age less than 18 and over 85 years old, class III heart failure, hepatic, renal failure, long-term use of anticoagulants, mechanical prosthetic heart valves, pregnancy, history of severe concomitant diseases (pulmonary tuberculosis, AIDS, HIV), alcoholic and/or drug addiction, diseases that cause hemolysis or instability of red blood cells, as well as acute infectious diseases during the examination.

The patients were separated into two groups depending on the comorbid burden. The first group (n=24) included patients with I (n=3) and II (n=21) degrees of risk of possible postoperative thrombohemorrhagic complications, the second (n=48) – with III (n=44) and IV (n=4) degrees of the risk.

To assess the influence of somatic pathology on the prognosis of the development of postoperative complications in patients, the Charlson comorbidity index was calculated [12]. When calculating the index, the ranking was carried out by age and the presence of concomitant diseases according to a point system. The resulting score index from 1 to 3 points corresponded to the low degree of risk of hospital postoperative complications (class I), the sum of points from 4 to 6 – moderate (class II), from 7 to 9 points – high (class III), 10 or more points – very high degree of risk (class IV) (tab. 1).

To assess the risk of developing and preventing THC at the stage of surgical treatment, the CRC patients were studied the hemostatic potential (HP) of the coagulation system in dynamics: before and after a functional test with double local ischemia of the upper limb (DLIUL), which allows to assess the reserve capabilities of the hemostasis system (HS) [4].

Evaluation of HP was carried out by the method of indirect piezothromboelastography (LFPTEG) with using a hardware-software complex for studying the rheological properties of blood ARP-01M “Mednord”, Russia, registration certificate FRS No. 2010/09767. Determination of HP was performed using the computer program “GEMO-3”, with the assessment of HS units: 1) vascular-platelet (initiation – A₀, amplification – t₁, intensity of contact coagulation – ICC); 2) coagulation (constant of thrombin activity – CTA, blood coagulation time – BCT (t₃), coagulation drive intensity – CDI, intensity of clot polymerization – ICP, maximum clot density – MCD); 3) fibrinolytic (intensity of retraction and clot lysis – IRCL).

Changes in HP parameters from the vascular-platelet link in the form of hypo/hyperaggregation, and/or from the coagulation link – in the form of hypo/hypercoagulation; and/or fibrinolytic – in the form of a decrease/increase in activity by less than 25.0 % of the initial value corresponded to the presence of a minimum degree of risk of developing THC (0 points), or a compensated reaction of HS. Changes in indicators on the part of each of the links within 25.1–50.0 % of the initial value indicated a subcompensated reaction and the presence of an average degree of risk of THC (1 point); within 50.1–

75.0 % – a decompensated reaction and a high degree of risk (2 points), and by more than 75.0 % – a depleted reaction of a very high degree of risk (3 points).

Table 1

Clinical characteristics of patients

Parameter	Total, n=72 (%)	Risk group based on the results of a functional test, n (%)		p ₁ to p ₂
		1 (I-II) 24 (33.3), (p ₁)	2 (III-IV) 48 (66.7), (p ₂)	
male	42 (58.3)	14 (19.4)	28 (38.9)	0.061
female	30 (41.7)	10 (13.9)	20 (27.8)	0.121
Age, years	61.6 [41.8; 81.4]	55.1 [51.4; 58.8]	66.1 [63.8; 68.3]	0.042*
Comorbidity index by Charlson, n (%)	72 (100)	24 (33.3)	48 (66.7)	0.082
class I	3 (4.2)	3 (4.2)	0	>0.1
class II	21 (29.2)	21 (29.2)	0	>0.1
class III	44 (61.1)	0	44 (61.1)	>0.1
class IV	4 (5.6)	0	4 (5.6)	>0.1
Complications, n (%)	6 (8.4)	1 (1.4)	5 (7.0)	0.077
purulent-septic	1 (1.4)	0	1 (1.4)	>0.1
eventration	2 (2.8)	0	2 (2.8)	>0.1
thrombosis	1 (1.4)	0	1 (1.4)	>0.1
hemorrhagic	2 (2.8)	1 (1.4)	1 (1.4)	>0.1
Stages TNM, n (%)	72 (100)	24 (33.3)	48 (66.7)	0.082
stage I	4 (5.6)	3 (4.2)	1 (1.4)	>0.05
stage II	26 (36.1)	9 (12.5)	17 (23.6)	>0.05
stage III	22 (30.5)	6 (8.3)	16 (22.3)	>0.05
stage IV	20 (27.8)	6 (8.3)	14 (19.4)	>0.05

Note:* – indicates that the difference is statistically significant compared to group 1 with group 2 (p<0.05)

Depending on the results obtained by LFPTEG, after the functional test for the correction of HS function, the patients were prescribed: Flexital (a drug that improves microcirculation, Pentoxifylline, Yuri-Pharm LLC, Ukraine), Bemiparin (low molecular weight heparin, Bemiparin, Berlin Chemie, Germany), Corvitan (a capillary stabilizing agent, Guercetinum, “Borshchahiv Chemical-Pharmaceutical Plant”, Ukraine), Vikasol (synthetic analogue of vitamin K, Vikasol, Pharmaceutical company “Darnitsa”, Ukraine), Sangera (fibrinolysis inhibitor, Tranexamic acid, “Lekhim-Kharkiv”, Ukraine).

The variational-statistical processing of quantitative data was carried out using the STATISTICA for Windows and Microsoft Excel (Microsoft Office 2010) programs on a personal computer. Determination of the numerical characteristics of indicators was carried out by the method of descriptive statistics as the number of observations, arithmetic mean, standard deviation, relative value. Verification of the studied aggregates for normal distribution was carried out using the Shapiro-Wilk test. The significance of differences in variables in samples with a normal distribution was assessed by the Student's t-test, and in the case of an abnormal distribution – by the Mann-Whitney U-test (the difference was considered significant at p<0.05). The limits of the 95 % confidence interval (95 % CI) were calculated [5].

Results of the study and their discussion. Of the 72 observed CRC patients in both groups aged 31–79 years (on average, 61.64±1.19 years), 58.3 % were men (42), 41.7 % were women (30). In the course of studying the comorbid status, it was found that most often CRC was accompanied by the development of CHF (56.7 %), less often it was accompanied by: peptic ulcer disease (16.7 % of cases), diabetes mellitus (16.7 %), chronic nonspecific lung diseases (13.3 %), collagenosis (3.3 %).

The primary tumor was localized in the rectum in 14 patients (19.4 %), in the sigmoid colon – in 17 (23.6 %), in the right sections of the colon – in 22 (30.6 %), in the rectosigmoid region – in 19 (26.4 %).

Due to the general initially severe comorbid status, laparotomy was performed in most patients; in total, laparoscopic surgical interventions were performed in 6.9 % of cases (in 5 patients). By the content of surgical intervention: more often (66.7 % of cases) radical operations were performed (including removal of the primary tumor focus and all distant metastases), less often – radical cytoreductive (including removal of the primary tumor focus and part of distant metastases – 16.7 %), palliative (6.6 %) and primary reconstructive surgical interventions (10.0 %).

In the studying group of patients, adenocarcinomas with a low grade of malignancy (G₁-G₂) were found in 93.3 % of cases, with a high grade (G₃) – in 6.7 %. In 4 (5.6 %) cases CRC was detected at stage I, in 26 (36.1 %) – at stage II, in 42 (58.3 %) – at late stages (stages III-IV) (tab. 1).

After a functional test, in accordance with the results of the study of the hemostatic potential, the CRC patients were divided into two groups. The first group included 24 (33.3 %) patients with compensated (I) and subcompensated (II) HS reactions, the second – 48 (66.7 %) patients with decompensated (III) and depleted (IV) HS reactions. Men in the first group accounted for 19.4 % (14), in the second – 38.9 % (28) ($p=0.06$), women – 13.9 % (10) and 27.8 % (20), respectively ($p=0.121$). The patients of the first group were significantly younger than those of the second group ($p=0.042$), the mean age was (55.1 ± 1.9) and (66.1 ± 1.1) years, respectively.

The risk of developing THC in the CRC patients increased with age ($r=0.72$; $p=0.042$). During the assessment of the risk of developing postoperative complications according to the Charlson comorbidity scale, low (class I) and moderate (class II) degrees of risk were identified in 23 (95.8 %) of 24 patients of the first group, high (class III) degree of risk – in 1 patient from the first and 44 patients from the second group, and very high (class IV) – in 4 patients of the second group. A high coefficient of conjugation was obtained between the risk class of somatic complications according to the Charlson comorbidity scale and the results of the study of HP according to the LFPTEG data ($r=0.69$; $p=0.012$). Considering the obtained results of ranking the CRC patients at the stage of preoperative preparation using two methods that allow to identify potential risks, both of a general somatic nature (the Charlson comorbidity scale) and from the hemostatic system (according to LFPTEG results), it is possible to recommend their combined use to determine the individual risk.

According to the Charlson comorbidity scale in CRC patients, the predicted relative risk (RR) of complications associated with the cardiovascular system (CVS) was $RR_{CVS}=2.9$, $p=0.016$, with the additional use of the results of DLIUL functional test, RR indicator increased ($RR_{CVS}=4.3$; $p=0.001$), the sensitivity of the assessment of predicted risks increased. During assessing THC on the Charlson comorbidity scale, the risk was low ($RR_{THC}=1.3$; $p=0.048$), during using the test results, it was high ($RR_{THC}=3.2$; $p=0.017$). Thus, the use of the LFPTEG results after the DLIUL functional test significantly increases the sensitivity of the Charlson rating scale in predicting the relative risks of complications of surgical treatment of the CRC patients associated with a comorbid state.

In 3 (4 %) patients of the first group, stage I of the disease ($T_{1-2}N_0M_0$) was diagnosed, in 9 (13 %) – stage II ($T_{3-4}N_0M_0$), in 6 (8 %) – III ($T_nN_{1-2}M_0$) and in 6 (8 %) – IV ($T_nN_nM_1$). Among the patients of the second group, stage I of the disease was detected in 1 (1 %) patient, stage II – in 17 (24 %), III – in 16 (22 %), IV – in 14 (20 %). In the patients of both groups, the risk of developing THC was associated with age ($r=0.72$; $p=0.042$) and stage of the disease ($r=0.56$; $p=0.049$).

In 44 CRC patients with high (III) and 4 with very high (IV) (58.4 ± 5.8) % risk on the Charlson comorbidity scale, a decompensated or depleted type of reaction of the hemostasis system was obtained during the DLIUL test ($r=0.69$; $p=0.012$). Compensated response was noted in 3 (4.2 ± 2.42) % of the CRC patients, subcompensated – in 21 (29.2 ± 5.4) %, decompensated – in 44 (55.6 ± 5.9) %, depleted – in 4 (5.6 ± 2.7) %.

As the underlying disease progresses, there is a “depletion” of the reserve capacities of HS: the total lytic and antithrombin activity caused by prolonged “stress” of its functional state in conditions of cancer progression, this indicates the insufficiency of the anticoagulant mechanisms of blood, being objective evidence of an increased risk of THC in these patients. In the CRC patients, more often with stages III–IV of the disease, the LFPTEG results after the functional test corresponded to the decompensated or depleted type of HS reaction ($r=0.59$; $p=0.036$) (tab. 2).

According to LFPTEG data, in patients to varying degrees (>25–75 %), deviations from the reference values (RV) of indicators characterizing the aggregation ability of platelets were revealed: A_0 – the initial indicator of the aggregate state of blood (specific units), $R(t_1)$ – time of the contact phase of coagulation (minutes), ICC – intensity of the contact phase of coagulation (specific units).

Therefore, A_0 in patients of the first group, on average, was (328.60 ± 10.16) specific units, which is 47.58 % higher than RV (222.25 ± 10.36) specific units, in patients of the second group – (391.77 ± 10.29) specific units, which is 76.27 % higher than RV.

With RV equal to (84.49 ± 16.96) specific units, ICC indices in the groups were (120.59 ± 2.34) and (133.29 ± 3.83) specific units, having increased by 42.73 % and 57.78 %, respectively, which indicates an increase in the activity of aggregation processes, what was more pronounced in patients of the second group. $R(t_1)$ in patients of the first and second groups was (1.64 ± 0.13) and (1.46 ± 0.12) seconds, respectively, which is 30.51 % and 38.14 % lower than RV (2.36 ± 0.11). An increase in the activity of A_0 , ICC and a decrease in $R(t_1)$ indicate an increase and acceleration of platelet aggregation in the CRC patients even before the start of surgical treatment. During the analysis of the function of the first (CTA – constant of thrombin activity (specific units), BCT – blood coagulation time (minutes), CDI – coagulation drive

intensity (specific units)) and the second (ICP – intensity of clot polymerization (specific units), MCD – maximum clot density (specific units)) of coagulation links, an increase in the amplitude and a shortening of the chronometric parameters of the hemostasiogram were also noted, indicating an increase in coagulation processes.

Table 2

LFPTEG results in patients after a functional test of the hemostasis system

Parameter	Group	M	SD	m	95 % CI		p
					lower limit	upper limit	
A ₀	reference values RV	222.25	68.70	10.36	201.95	242.55	<0.0001
	I (n=24)	328.60	67.40	10.16	308.69	348.52	
	II (n=48)	391.77	68.26	10.29	371.60	411.94	<0.0001*
t ₁	RV	2.36	0.72	0.11	2.15	2.57	0.0004*
	I (n=24)	1.64	0.88	0.13	1.38	1.90	
	II (n=48)	1.46	0.80	0.12	1.22	1.70	<0.0001*
ICC	RV	84.49	16.96	2.56	79.48	89.50	<0.0001*
	I (n=24)	120.59	15.54	2.34	116.00	125.19	
	II (n=48)	133.29	25.42	3.83	125.77	140.80	<0.0001*
CTA	RV	15.25	2.02	0.30	14.66	15.85	<0.0001*
	I (n=24)	29.50	4.19	0.63	28.26	30.73	
	II (n=48)	41.12	11.34	1.71	37.77	44.47	<0.0001*
BCT	RV	8.42	1.35	0.20	8.03	8.82	<0.0001*
	I (n=24)	3.57	1.29	0.19	3.19	3.95	
	II (n=48)	2.78	1.22	0.18	2.42	3.14	<0.0001*
CDI	RV	21.15	3.23	0.49	20.19	22.10	<0.0001*
	I (n=24)	35.39	5.92	0.89	33.64	37.14	
	II (n=48)	45.74	11.63	1.75	42.31	49.18	<0.0001*
ICP	RV	14.46	1.25	0.19	14.09	14.83	<0.0001*
	I (n=24)	20.84	2.33	0.35	20.15	21.53	
	II (n=48)	23.02	3.62	0.55	21.95	24.09	<0.0001*
MCD	RV	525.46	95.51	14.40	497.24	553.68	<0.0001*
	I (n=24)	802.52	63.76	9.61	783.68	821.36	
	II (n=48)	811.03	79.97	12.06	787.40	834.66	<0.0001*
IRCL	RV	16.46	2.59	0.39	15.69	17.23	<0.0001*
	I (n=24)	7.53	1.01	0.15	7.23	7.82	
	II (n=48)	5.02	0.79	0.12	4.79	5.25	<0.0001*

Note:* – indicates that the difference is statistically significant when compared with reference values (p<0.05)

In the CRC patients of the first and second groups, an increase in CTA was established to (29.50±0.63) and (41.12±1.71) specific units, which, respectively, by 1.9 and 2.7 times higher than RV (15.25±0.30). CDI was (35.39±0.89) and (45.74±1.75) specific units, respectively, which is 67.33 % and 116.26 % higher than RV (21.15±0.49). ICP – (20.84±0.35) and (23.02±0.55) specific units, respectively, which is by 44.12 % and 59.20 % higher than RV (14.46±0.19). A decrease in BCT (T₃) was established to (3.57±0.19) and (2.78±0.18) minutes, which, respectively, 2.4 and 3 times less than RV (8.42±0.20). MCD was (802.52±9.61) and (811.03±12.06) specific units, which exceeded RV (525.46±14.40) by 52.73 and 54.35 %, respectively.

The indicator characterizing the fibrinolytic activity of the blood serum – the intensity of retraction and lysis of the clot (IRLC, specific units), – as the final stage of the functioning of the hemostasis system, was significantly lower in individuals of both groups – (7.53±0.15) and (5.02±0.12) specific units, respectively, what in 2.2 and 3.3 times lower than RV (16.46±0.39), indicating a reduced function of fibrinolysis. Thus, the obtained results of LFPTEG in the CRC patients of the both groups indicate an increase in the processes of aggregation and coagulation and, at the same time, a decrease in fibrinolytic activity, emphasizing the presence of risks of developing THC. Depending on the obtained results of studying the comorbid status and reserve capabilities of the hemostasis system in the CRC patients in the pre-, peri- and postoperative period, different schemes for the prevention of THC were used (fig. 1).

Patients of the second group with a high (III) degree of risk of developing complications, with a decompensated type of reaction from the vascular-platelet link were prescribed 100 mg of Flexital intravenously once a day. If the patient had decompensation from the coagulation link, he was prescribed low molecular weight heparin (LMWH) – Bemiparin at a dose of 2,500 units once a day subcutaneously. Currently, LMWH are the basis for specific prophylaxis of THC in cancer patients [9]. According to the recommendations of medical oncologists (HeSMO) [12], when carrying out major surgical interventions

on the abdominal cavity and small pelvis, patients are recommended to carry out antithrombotic prophylaxis using LMWH within 4 weeks after the operation in case of additional risk factors.

Reaction type	Hyperaggregation + normocoagulation	Normoaggregation + hypercoagulation	Hyperaggregation + hypercoagulation	Hyperaggregation + Hypocoagulation
Compensated	No correction	No correction	No correction	No correction
Subcompensated	No correction	No correction	No correction	No correction
Decompensated	100 mg of Flexital per 400 intravenously once a day	2,500 units of Bemiparin once a day	Flexital + 2,500 units of Bemiparin once a day	Flexital + Vikasol
Depleted	100mg of Flexital intravenously twice	2,500 units of Bemiparin once a day	Flexital + 2,500 units of Bemiparin once a day +0.5g of Corvitin per 100 ml of saline	Flexital + Vikasol + 0.5g of Corvitin per 100 ml of saline

Fig. 1. Scheme for the prevention of thrombohemorrhagic complications in patients with colorectal cancer, depending on the results of the DLIUL test

Patients with a decompensated type of reaction from both the vascular-platelet link (hyperaggregation) and the coagulation link (hypercoagulation) were injected with both medications. If changes in the form of hypocoagulation were obtained from the side of the coagulation unit, 1.0 % solution of Vikasol was also injected intramuscularly.

Patients with a high (III) and very high (IV) degrees of risk of complications and with a depleted type of reaction of the hemostasis system from the vascular-platelet link were prescribed 100 mg of Flexital intravenously once a day. If a patient had a depleted type of reaction from the coagulation link towards hypercoagulation, he was prescribed 2,500 units of Bemiparin subcutaneously once a day. If a patient had a depleted type of reaction from both the vascular-platelet link (hyperaggregation) and the coagulation link (hypercoagulation), in addition to Flexital and Bemiparin, he was additionally injected with 0.5 g of Corvitin intravenously. If the patient has hypocoagulation, he was injected with 1.0 % solution of Vikasol intramuscularly and Corvitin – intravenously.

In the patients of both groups, the total proportion of postoperative complications was 8 %, including in 1 patient of the first group and in 5 patients of the second group ($p=0.077$). HC in the early postoperative period were detected in 2 (3 %) of the patients: acute erosive bleeding in a patient of the first group and coagulopathic bleeding (against the background of initial hypoproteinemia and resection of liver segments affected by metastases) in a patient of the second group. An incisional hernia of the midline laparotomic wound developed in 2 (3 %) of the patients, purulent-septic complications – in 1 (1 %) of the patients, VTEC – pulmonary embolism – in 1 (1 %) of the patients.

The high efficacy of using the results of low-frequency piezothromboelastography along with the study of the comorbid status in assessing the risks of adverse events in the surgical treatment of patients with CRC was found. Thus, with the additional use of the hemostatic potential results, the THC relative risk index was significantly higher than with the risk assessment only using the Charlson scale (from 1.3 to 3.2; $p=0.017$). Low molecular weight heparin (bemiparin) was used to prevent THC in the surgical treatment of colorectal cancer patients [14], the selection of other drugs was carried out depending on the results of the dynamics of hemostatic potential indicators, which were controlled by repeated studies in the early postoperative period and on the 3rd day after the operation. In our study, control of the hemostatic system parameters and the use of a complex correction scheme in an individual patient made it possible to reduce the incidence of thrombosis (1.4 %). While the authors report, despite the use of low molecular weight heparins, the incidence of VTEC in the surgical treatment of colorectal cancer, according to Nakagawa K, reached 7.5 % of cases [10], as reported by Lu X. et al. – in 7.8 % [9]. According to Osaki T. [11] in the postoperative period in patients with gastric cancer VTEC developed in 7.2 % of cases, according to Kaida S. [8] – in 4.0 % of patients (1.6 % with symptoms and 2.4 % without symptoms) within 7 days after surgery for stomach cancer, Suzuki S. [13] indicates 4.3 % of hemorrhagic complications.

Several authors reported that the prevalence of VTEC is higher in older patients than in younger patients [8, 10, 12]. In the present study, we also showed that as patients with CRC get older ($r=0.72$; $p=0.042$) and as their underlying disease progresses ($r=0.56$; $p=0.049$), they the risk of developing THC increases. In conditions of cancer progression, there is a “depletion” of the reserve capabilities of the patient's hemostasis system (general lytic and antithrombin activity, insufficiency of the anticoagulant mechanisms of the blood develops, which increases the risk of THC in the patient).

According to Lu X. et al. [9] in all patients, the risk indicators of VTEC according to the Caprini scale were higher than 5 points. The high-risk subgroup (≥ 12 points) was 40.5 %. In the present study, the Chalsion scale was used, supplemented with thromboelastogram indicators, the high-risk subgroup (≥ 12 points) was 66.7 %. The differences were statistically significant ($p=0.02$). Using a functional test with double local ischemia of the upper limb, the reserve capabilities of the hemostasis system of patients with CRC were studied, which made it possible to identify a risk group of THC and apply complex correction schemes (including: antiplatelet agents, direct anticoagulants, bioflavinoids, cofactors of coagulation system components, antifibrinolytic drugs) in surgical treatment.

To prevent coagulopathic bleeding, it is necessary to use dynamic monitoring of the hemostasis system using laboratory (complete blood count, coagulogram) and highly informative instrumental research methods (LFPTEG), the results of which will determine the dosage and time of prescribing anticoagulants to the patients, and, if necessary, the abolition of anticoagulants due to risk bleeding.

Conclusions

1. A comprehensive assessment of the relative risk of complications of surgical treatment of patients with CRC is more indicative of the results of the study of hemostatic blood potential than in the assessment of risk only on the Charlson scale (1.3 vs. 3.2; $p = 0.017$).

2. As the CRC patients grow older ($r=0.72$; $p=0.042$) and as their underlying disease progresses ($r=0.56$; $p=0.049$), their risk of developing THC increases: under conditions of cancer progression, there is a “depletion” of reserve the capabilities of the patient's hemostasis system (total lytic and antithrombin activity, insufficiency of the anticoagulant mechanisms of the blood develops, which increases the risk of THC in the patient).

3. The use of complex correction schemes (including: antiplatelet agents, direct anticoagulants, bioflavinoids, cofactors of the components of the coagulation system, antifibrinolytic drugs) during the surgical treatment of the CRC patients with high (III) and very high (IV) degrees of risk of thrombohemorrhagic complications significantly reduced the incidence of the development of VTEC (1 %) and HC (3 %) in the postoperative period.

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