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Correction of endothelial dysfunction in patients with pancreatic head cancer and its clinical outcome

95 operated patients with cancer of the head of the pancreas of clinical stages II and III were examined to analyse the changes in endothelial function after surgery against correction. Function indicators of endothelium and circulating endothelial content were tested.

The use of L-arginine and ACE inhibitor in complex treatment decreased the endothelium damage and supported the correction of endothelial dysfunction. The developed methods of treatment were also associated with fewer complications.

Keywords: pancreatic head cancer; endothelial dysfunction; L-arginine; inhibitor of the angiotensin-converting enzyme.

Introduction. The general state of the body plays an important role in determining the outcome of surgical and conservative treatment of malignant neoplasms [1-3]. This condition is determined by the presence or absence of disorders of system and regional hemodynamics, breathing, functioning of the indicators of biochemical systems, production and utilization of hormones, and etc. [4, 5]. A universal aspect in this case is the functioning of vascular endothelium depending on its morphology, also in the tumour.

Microenvironment of endothelium in tumour tissue, chronic hypoxia of endotheliocytes, frequent vascular injury determine the formation of system mechanisms aimed at activation of vascular-platelet haemostasis, vasoconstriction, the production of growth factors and inflammatory cytokines [6].

Growth of the pancreatic cancer head is usually associated with severe metabolic disturbances, the intoxication syndrome, malabsorption and maldigestion that worsen the overall condition of the patients and increase the risk of negative treatment outcome [7]. Under these conditions, the improvement of systemic parameters of blood circulation can significantly improve the surgical treatment outcome.

Purpose of the study: analysis of changes in endothelial function in patients with pancreatic head cancer after surgery against a background of correction.

Materials and methods. 95 patients with Stage II (T3N0M0 (2a), T1-3N1M0 (2b)) and Stage III (T4N1M0) pancreatic head cancer (45 and 50 patients, respectively), of them, 66 men and 29 women aged 40 to 65 (mean age 60.8 ± 2.1 years) were examined. All patients underwent combined therapy including radical surgical treatment in the form of gastro- pancreatoduodenectomy or pancreatoduodenectomy.

Patients with severe comorbidities were excluded from the study. An obligatory criterion for inclusion was the informed consent of patients for the administration of additional methods of conservative treatment and the anonymous use of the findings in the scientific study.

All patients were divided into two groups by the use of additional perioperative therapy aimed at the correction of endothelial dysfunction. The patients in different groups had no significant discrepancies in terms of age, sex, stage of neoplasm, tumour localization in the stomach, the severity of condition in preoperative period, the concomitant diseases and the conducted surgical interventions.

The control arm included 40 practically healthy individuals aged 40 to 65 (mean age 57.3 ± 2.0 years).

The studied indices of vascular endothelial function included: the content of desquamated (circulating) endotheliocytes in the blood (CE), the von Willebrand factor (vWF) in plasma and the degree of endothelium-dependent vasodilation (EDVD) [8].

Clinical results were reviewed to detect purulent-septic, thrombotic complications early postoperatively and prospectively (2.1 ± 0.1 years in the treatment arm and 2.0 ± 0.2 years in the comparison arm).

Additional therapy aimed at the correction of endothelial dysfunction included L-arginine (vasoton, Barnaul, R.F.) 1.0 g 1/1with ACE inhibitor (enalapril) 5 mg 1/1. The therapy started 3-4 days pre-surgery. Contraindication for ACE inhibitor was the expressed arterial hypotension (systolic pressure below 90 mmHg). Patients with such hemodynamics were excluded from the study.

The statistical significance of differences in indicators in groups and in dynamics was estimated by Mann-Whitney using the bootstrap method [9].

Results. The top line findings of the analysis of indicators in patients with pancreas head cancer are presented in Figures 1-3.

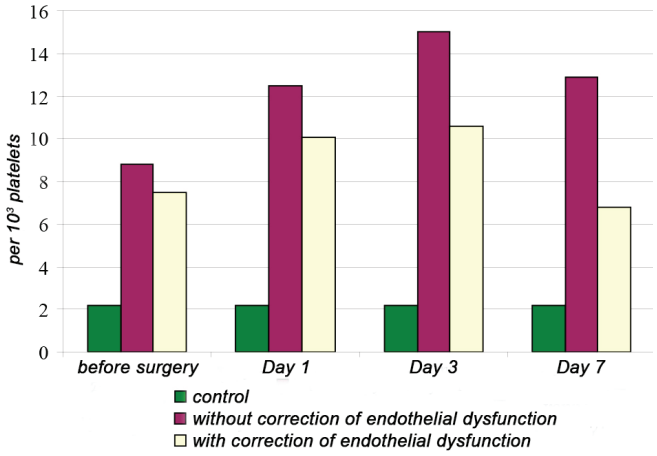

Figure 1 – Comparative analysis of the median content of circulating endotheliocytes in patients with pancreatic head cancer

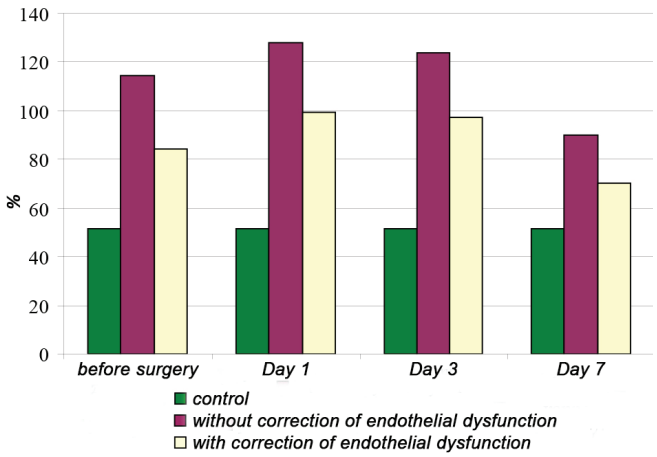

Figure 2 – Comparative analysis of the median value of von Willebrand factor in patients with pancreatic head cancer

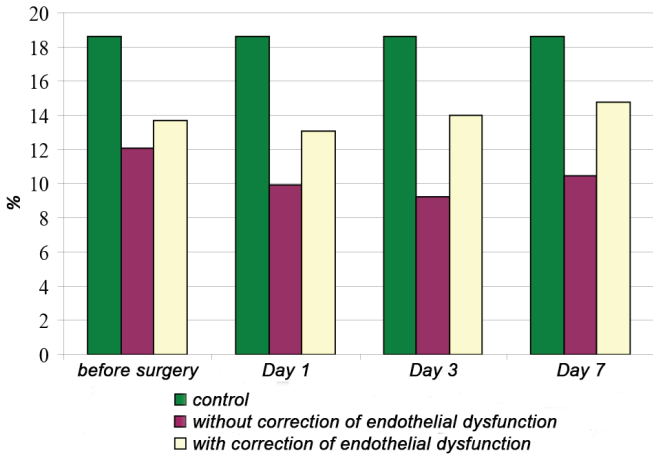

Figure 3 – Comparative analysis of the median value of von Willebrand factor in patients with pancreatic head cancer

There were some statistically significant deviations in vascular endothelial parameters from the values in the control arm both before and after the surgery in dynamics. The CE value sharply exceeded the control values at the outcome (Me/Me = 3.41), with the highest values on Day 3 after surgery (Me/Me = 4.82), and a decrease on Day 7 (Me/Me = 3.09, p <0.01 in all cases).

The groups of patients with pancreatic head cancer selected depending on the treatment differed in the CE value from Day 1 after surgery. The differences were statistically significant (Me/Me = 1.28, p <0.05) and have increased on Day 3 (Me/Me = 1.56, p <0.05) and Day 7 (Me/Me = 1.91, p <0.01). As in the previous group, we detected the protective effect of conservative treatment performed before surgery on the level of damage to the vascular endothelium.

This is proven by the analysis of von Willebrand factor (vWF) in blood. Before the surgery, that indicator was relatively higher vs. control arm (Me/Me = 1.63), with the highest value on Day 1 (Me/Me = 1.92), and the same downward trend afterwards. On day 7, the difference with the control arm was 1.36 times (p <0.05 in all cases).

On Day 1 after surgery, the vWF content in the comparison arm was higher compared to the treatment arm (Me/Me = 1.21, p <0.05). On Day 3, the difference remained at the same level (Me/Me = 1.28, p <0.05); on Day 7 it increased up to Me/Me = 1.54 (p <0.05) due to more rapid dynamics of compensation in the treatment arm.

The EDVD level in the comparison arm was decreasing after surgery. In the treatment arm, on the contrary, the differences of the values with the control arm on Day 7 days were less than at the outbreak of the study. The most significant differences in that indicator were registered on Day 1 after surgery (RR = 1.42, p <0.05).

At the outcome, there were no statistically significant differences between the arms. The difference increased one day after surgery (Me/Me = 1.36, p <0.05). On Day 3, the differences between the arms reached the maximum level of RR = 1.55 (p <0.05). On Day 7 the difference between the groups of patients with pancreatic head cancer has decreased, but was still statistically significant (Me/Me = 1.42, p <0.05).

Table 1 presents the clinical results of treatment of patients depending on the received therapy.

The differences in the relative rates of complications in the early postoperative period were relatively moderate, but still statistically significant (RR = 1.75, p <0.05 for Stage II, and RR = 1.70, p <0.05 – for Stage III of pancreatic head cancer).

In contrast, 2 years of prospective follow-up revealed very significant differences in the incidence of relapse and metastasis: for the clinical stage II – up to RR = 2.63, p <0.05, and for the clinical stage III – RR = 2.34, p <0.05. The low level of statistical significance was associated with a small number of complications in the treatment arm.

Table 1 - Treatment outcome of patients with pancreatic head cancer

Indicator	Patient arms				
	Treatment arm (n = 44)		Comparison arm (n = 51)		P
	abs. number	%	abs. number	%	
Presence of complications in early postoperative period	10	22,7	20	39,2	>0,05
Presence of relapses and / or metastases	7	15,9	20	39,2	<0,05

Conclusion. The patients with pancreatic head cancer involved in the study had significant dysfunction of the vascular endothelium manifested by the increase in the content of circulating endotheliocytes which evidences the damage to the endothelium [10] and the reduction in vasodilating and anti-aggregatory properties. These changes were clinically proven. Expressed endothelial dysfunction led to a significant increase in the number of complications in the early postoperative period.

The use of additional therapy with the combination of L-arginine and an ACE inhibitor aimed at the correction of endothelial dysfunction contributed to a reduction in the number of complications what should be associated with the correction of endothelial dysfunction. Patients in the treatment group had less damage to the endothelium what was confirmed by a significant decrease in the number of circulating endotheliocytes, the content of pro-aggregate von Willebrand factor, and the increase in the endothelium-dependent vasodilatation index.

These changes could promote the improvement of condition of microcirculatory bed in the area of anastomosis and, moreover, the permeability of the blood channel at the level of arteries of medium diameter. It also corresponds to the results obtained by other authors [11, 12].

In general, the obtained results testify to the possibility of using the developed method of treatment in a complex of perioperative management of patients with pancreatic head cancer as well as with other neoplasms of the gastrointestinal tract.

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