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DYNAMICS OF THE SERUM BILIRUBIN LEVEL DURING BILE DUCTS DRAINAGE IN PATIENTS WITH HILAR TUMOR STENOSIS AND JAUNDICE

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Abstract

Palliative bile duct decompression with various modifications are currently performed in 75-80% of patients with hilar stenosis caused by the tumor. The main goal of palliative care is to reduce the manifestations of jaundice, intoxication, pain syndrome, prolong life period and improve patient's conditions for chemotherapy.

Objective: to evaluate the effectiveness of bile ducts antegrade drainage methods by bilirubin reducing in the palliative treatment of patients with jaundice due to hilar stenosis caused by the tumor.

Materials and methods. In a prospective study included 78 patients with hilar obstructive jaundice, who were underwent of palliative antegrade draining of bile ducts: percutaneous transhepatic cholangiostomy (group PTC) - n = 24, externally-internal suprapapillary cholangiostomy (group EISC) - n = 26, percutaneous transhepatic antegrade endobiliary stenting (group PTAES) - n = 28. Endpoints of the study: total serum bilirubin before the procedure, after 3, 7 days and every 10 days for two months. The mean values of bilirubin and the average percentage of decrease in its value at each of the control periods were evaluated in relation to the initial level. Also, at the same time, the cumulative percentage of patients in which bilirubin had a value of ≤34.2 μmol / L (2 mg / dL) or ≤ 85.5

μmol / L (5 mg / dL) was assessed - the threshold values at which a certain type of chemotherapy is possible.

Results. In all groups, there was a decrease in the average values of bilirubin levels with an increase in the time passed after the procedure. At all control periods, the mean bilirubin values and the percentage of decrease in the mean bilirubin values did not differ statistically between groups (all $p < 0.05$). The highest rates of decrease in the level of bilirubin were observed during the first 10 days (about 60.0%). From the 10th to the 60th day, the decrease in the level of bilirubin was approximately 20% from the initial one. The cumulative percentage of patients with the bilirubin level on the 60th day ≤ 34.1 μmol / l (2 mg / dl) was 45.8% in the EISC group, 64.5% in the PTC group, and 63.9% in the PTAES group ($p = 0.257$) in a month these indicators were 11.7%, respectively; 12.5% and 17.9% (all $p <0.05$). The decrease in the level of bilirubin ≤ 85.5 μmol / L (5 mg / dL) was more rapid. So, already after 10 days, the cumulative percentage of such patients in the groups exceeded 50.0%: 58.3% in the EISC group, 63.6% in the PTC group, 57.7 % in the PTAES group ($p = 0.26$) in a month these indicators were respectively 83.3%; 77.3% and 80.8%, after two months, respectively 91.7%, 86.4 and 100% ($p = 0.80$).

Conclusions. The methods of transcutaneous bile ducts drainage/stenting effectively reduce the level of total bilirubin in patients with obstructive jaundice due to hilar stenosis caused by tumor and have no statistically significant differences in the dynamics of bilirubin level within two months of observation.

Keywords: **obstructive jaundice; Klatskin tumor; externally-internal suprapapillary cholangiostomy; percutaneous transhepatic cholangiostomy; antegrade endobiliary stenting.**

Introduction. At admission to the hospital, the majority of patients with hilar stenosis and jaundice syndrome have locally advanced cholangiocarcinoma or metastatic cancer, and only 20% - 25% of them are eligible to radical treatment [1, 2]. Therefore, palliative bile duct decompression is currently the main method of treatment for such patients [3]. The main goal of palliative care is to reduce the manifestations of jaundice, intoxication, pain syndrome and prolongation of life period [4]. A decrease in the level of serum bilirubin also improves conditions for chemotherapy [5].

At high biliary tract blocks caused by tumor, it is usually performed with antegrade (percutaneous transhepatic) and retrograde (endoscopic) drainage or stenting. Now the

antegrade approach is considered more rational [6 - 8] at the same time there is enough comparative assessment of its individual methods for eliminating jaundice syndrome.

The work **aimed** to evaluate the effectiveness of antegrade methods of bile duct drainage in reducing bilirubin level in palliative treatment of patients with jaundice syndrome due to hilar stenosis.

Materials and methods. The prospective study included 78 patients with obstructive jaundice caused by proximal organic stenosis of the bile ducts. To reduce jaundice syndrome all patients underwent palliative antegrade drainage of bile ducts, including percutaneous transhepatic cholangiostomy - 24 (group PTC), 26 - externally-internal suprapapillary cholangiostomy (group EISC), 28 - percutaneous transhepatic antegrade endobiliary stenting (group PTAES).

The eligible criteria in the study were the presence of jaundice, the age of both sex patient more than 18 years, and the impossibility of performing radical surgery.

The exclusion criteria of the study were bile ducts mechanical obstruction without jaundice syndrome, the age of the patients less than 18 years, a high anesthetic risk - ASA 4 [9], multiple metastatic lesions of the liver, ascites, hemorrhagic diathesis, the presence of inflammatory diseases of the lungs and urinary tract, presence of coagulopathy (INR > 1.5).

The endpoints of the study were values of total bilirubin for two months after the procedure in the control periods: before the procedure, after 3, 7 days and every 10 days. The mean values of bilirubin and the average percentage of decrease in its value at each of the control periods were evaluated in relation to the initial level. Also, at each time frame, the cumulative percentage of patients in which bilirubin had a value of $\leq$ 34.2 μmol / L (2 mg / dL) or $\leq$ 85.5 μmol / L (5 mg / dL) was assessed - the threshold values at which a certain type of chemotherapy is possible [10, 11].

The intervention was considered technically successful if the drainage or stent was located in the intended area of the affected segment of the biliary tract and ensured successful drainage of bile through the drained/stented ducts.

All the patients received prophylactic antibiotics - 12 hours before the procedure, and 48-72 hours after it (cefuroxime 1.5 g and metronidazole 500 mg).

For EISC group patients cholangiostomy was performed under US and X-ray control by standard technique [12, 13] using the mini - pig drainage 9 Fr diameter. To prevent drainage blockage, the patients were recommended to sanitize it with 20 ml of saline twice a day.

Bile duct stenting was performed in patients of the PTAES group in two stages. The first stage was percutaneous cholangiostomy through the liver. After forming the external biliary fistula, for determining a location of the stent length and diameter control, cholangiogram was performed. Through the drainage canal, a metal nitinol uncoated stent was placed. After successful stenting, the percutaneous transhepatic through drainage catheter was removed [14].

The length of the nitinol stents was selected based on cholangiography data, focusing on the distance from the proximal edge of the narrowing to the orifice of the common bile duct, adding 2-3 cm to the obtained length.

Statistical processing of the obtained data was performed using the statistical package IBMSPPS Statistics 22. Descriptive statistics were performed. Evaluation of normal distribution of variables was performed by using a Shapiro-Wilk's method. Comparison of two independent groups for one quantitative trait was carried out using the Mann-Whitney method; comparison of the groups for a qualitative trait was performed using the Pearson χ^2 method. The analysis of the relationship between the two variables was carried out using linear regression analysis. The Kaplan-Meier method was used to assess survival. Comparisons of factor levels were performed using the log-rank test. The null hypothesis of equality of variables was rejected at $p < 0.05$.

Results

Patients in the study groups did not differ significantly in average age, sex, distribution of patients by the stage of the oncological process and TNM criteria.

According to obtained data, in the groups with antegrade stenting there was a smaller percentage of patients with tumors stage IV, compared with patients who underwent drainage of the bile ducts. At the same time, the distribution of patients by the stage of the process differed at the level of statistical significance ($p = 0.03$) between the patients of the PTAES and PTC groups.

The causes for the high block of the biliary tract in both groups were mainly Klatskin tumors and, less often, metastases of tumors of the abdominal cavity organs (stomach or intestines). For causes of high biliary tract block, the groups were statistically identical, $p = 0.89$, table. 2.

Table 1

Age, sex and distribution of patients according to the stage of the oncological process and TNM criteria in the study groups

Indicator	Group			P between groups		
	EISC (1) n=26	PTAES (2) n=28	PTC (3) n=24	1/2	1/3	2/3
Age, years (M±m)	60.4±1.6	62.9±2.3	63.3±1.7	0.087	0.258	0.904
Sex, m/f	12/14	12/16	11/13	0.419	0.571	0.829
T						
T2, n (%)	1 (3.8)	3 (10.7)	3 (12.6)	0.061	0.452	0.032
T3, n (%)	14 (53.8)	21 (75.0)	10 (41.7)			
T4, n (%)	11 (42.3)	4 (14.3)	11 (45.8)			
N						
N0, n (%)	3 (11.5)	2 (7.1)	1 (4.2)	0.680	0.640	0.928
N1, n (%)	16 (61.5)	18 (64.3)	17 (70.8)			
N2, n (%)	1 (3.8)	2 (7.4)	2 (8.3)			
Nx, n (%)	6 (23.1)	6 (21.4)	4 (16.7)			
M						
M0, n (%)	18 (69.2)	20 (71.4)	13 (54.2)	0.860	0.273	0.198
M1, n (%)	8 (30.8)	8 (286)	11(45.9)			
Stage						
IIA, n (%)	0 (0)	1 (3.6)	1 (4.2)	0.061	0.292	0.527
IIB, n (%)	0 (0)	2 (7.1)	2 (8.3)			
III, n (%)	8 (30.8)	15 (53.6)	8 (33.3)			
IV, n (%)	18 (69.2)	10 (37.5)	13 (54.2)			

Table 2

Distribution of patients in groups due to mechanical jaundice

Indicator	Group			P between groups		
	EISC (1) n = 26	PTAES (2) n = 28	PTC (3) n = 24	1/2	1/3	2/3
Klatskin tumor. n (%)	21 (80.8)	22 (78.6)	19 (79.2)	0.841	0.887	0.754
Mts . n (%)	5 (19.6)	6 (21.4)	5 (20.8)			

There were no significant differences between the groups for the distribution of hilar cholangiocarcinoma categories according to Bismuth H., Corlette M.B. [15] p = 0.14, table. 3.

The average values of the bilirubin level for the mini-invasive procedure in the EISC group were 196.8 ± 13.4 μmol / L (from 77.2 μmol / L to 333.1 μmol / L); in the PTC group - 207.7 ± 19.4 μmol / L (from 66.8.0 μmol / L to 301.1 μmol / L); group PTAES - 195.1 ± 11.5 μmol / L (from 69.2 μmol / L to 331.2 μmol / L); the median values of bilirubin were 203.0 μmol / L, 230.0 μmol / L and 194.0 μmol / L, respectively (all $p < 0.05$, Fig. 1).

Table 3

Distribution of patients with cholangiocarcinoma by Bismuth H., Corlette M.B.

Indicator	Group			P Between groups		
	EISC (1) n = 21	PTAES (2) n = 22	PTC (3) n = 19	1/2	1/3	2/3
1. n (%)	5 (23.8)	5 (21.7)	3 (15.8)	0.668	0.137	0.506
2. n (%)	2 (9.5)	5 (21.7)	8 (42.1)			
3A. n (%)	8 (38.1)	9 (39.1)	6 (40.0)			
3B. n (%)	5 (23.8)	4 (17.4)	1 (6.1)			
4. n (%)	1 (4.8)	0 (0.0)	1 (0.0)			

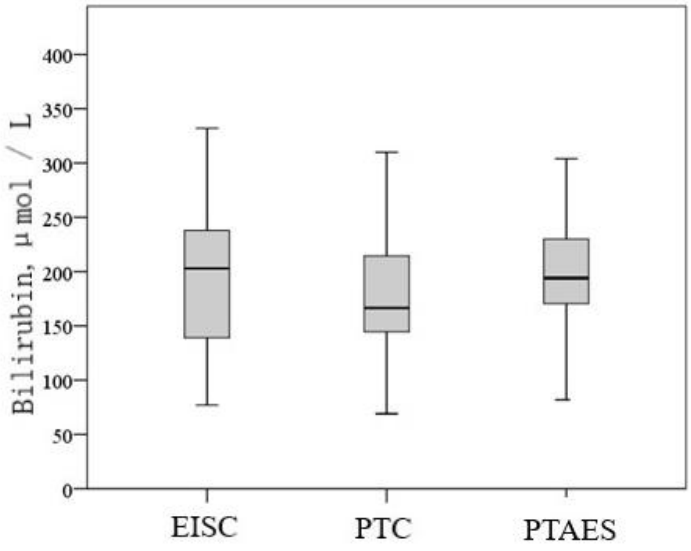

Figure 1. Medians and interquartile intervals of bilirubin levels before manipulation

The duration of jaundice in patients of the EISC group was on average 16.8 ± 0.5 days (from 14 days to 24 days), in patients of the PTAES group - 17.6 ± 0.4 days (from 13 days to 21 days)), in patients of PTC group - 17.7 ± 0.7 days (from 9 days to 23 days), p = 0.269 (all p <0.05).

The distribution of patients in groups according to the frequency of drainage (stenting) of different parts of the bile ducts are shown in table 4.

The frequency of drainage (stenting) of different parts of the bile ducts did not differ significantly between groups (all p <0.05, table 4). In all patients, more than 50% of the liver was drained. The distribution of the percentage of drained liver groups did not differ statistically (p> 0, 05, table 5).

Table 4

Distribution of patients in groups according to the frequency of drainage/stenting of different parts of the bile ducts

Indicator	Group			P between groups		
	EISC (1) n = 26	PTAES (2) n = 28	PTC (3) n = 24	1/2	1/3	2/3
Right hepatic duct. n (%)	9 (36.0)	13 (46.4)	9 (50.0)	0.391	0.727	0.923
Left hepatic duct. n (%)	9 (36.0)	9 (32.1)	6 (33.3)			
Common bile duct. n (%)	7 (28.0)	6 (21.4)	3 (16.7)			

Table 5

Distribution of patients in groups by percentage of drained liver

Percentage of drained liver	Group			P between groups		
	EISC (1) n = 26	PTAES (2) n = 28	PTC (3) n = 24	1/2	1/3	2/3
55. n (%)	10 (38.5)	9 (32.1)	5 (20.8)	0.855	0.593	0.797
75. n (%)	10 (38.5)	11 (39.3)	12 (50.0)			
100. n (%)	6 (23.1)	8 (28.6)	7 (29.2)			

The technical success of minimally invasive procedures, which was determined in the case of placement of the drainage tube in biliary ducts was 100% in all groups.

In all groups, there was a decrease in mean bilirubin levels with increasing duration of time after the procedure. In all control periods, the average values of bilirubin did not differ statistically between groups (all p <0.05, Fig. 2).

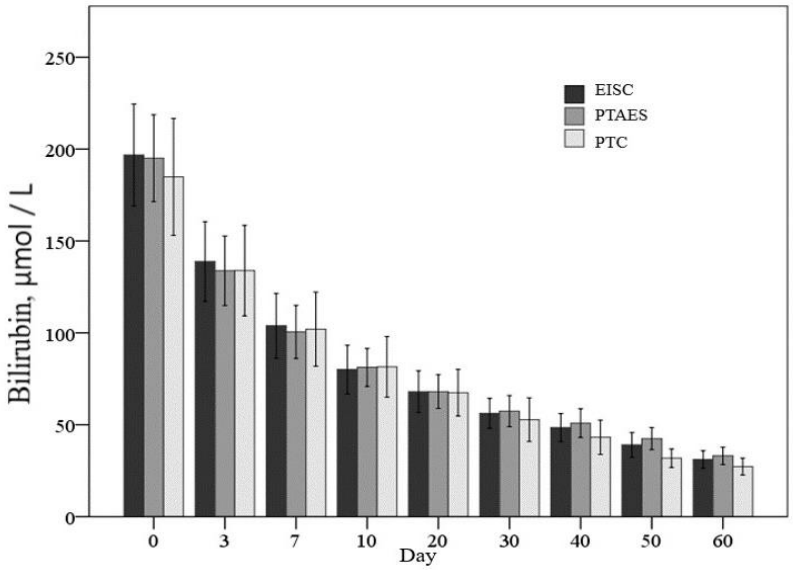

Figure 2. Dynamics of mean values of bilirubin (M; 95% CI) during the observation period in the study groups

In addition, there were no statistical differences between the groups in the percentage reduction in mean bilirubin values in the control periods of the study relative to baseline levels (all p> 0.05, Fig. 3).

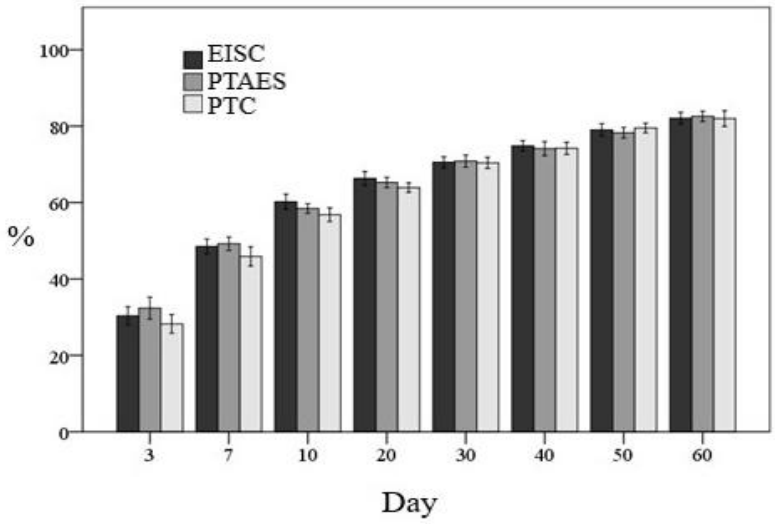

Figure 3. The percentage decrease in the average value of bilirubin in the control period relative to baseline levels in the groups

It is noteworthy that in all groups the greatest rate of decrease in bilirubin was observed during the first 10 days (about 60.0%). From the 10th to the 60th day, the decrease in bilirubin levels occurred by approximately 20% from baseline.

Given the unidirectional trends in the dynamics of bilirubin in the groups, we studied the dependence of the percentage decrease in bilirubin in each observation period from the initial values of bilirubin together in all groups using linear regression analysis, table 6.

Table 6

Coefficients of linear determination (R2) of dependence of percentage of decrease in bilirubin in control terms of research on initial values of bilirubin

Indicator	Observation period, days							
	3	7	10	20	30	40	50	60
R^2	0.101	0.204	0.113	0.045	0.060	0.044	0.011	0.196

In all control terms, the coefficients of linear determination (R^2) were low, which indicated the absence of a relationship between the decrease in the percentage of bilirubin and its initial values, Fig. 4.

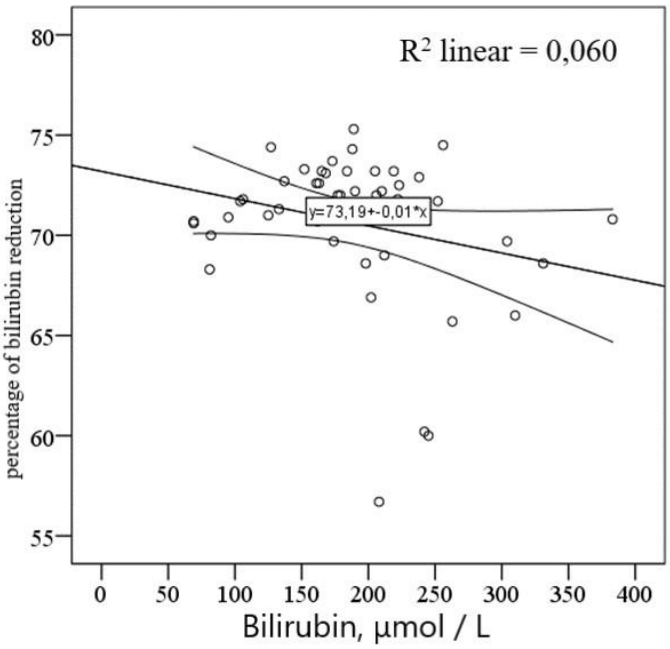

Figure 4. Diagram (scattering) with a 95% confidence interval of the percentage of bilirubin reduction one month after bile duct drainage from the ascending bilirubin values

Therefore, the percentage decrease in bilirubin relative to the ascending was approximately the same at high and low values, so the achievement of control values was faster at lower absolute values of bilirubin.

The cumulative percentage of patients in whom the level of bilirubin on the 60th day of the study reached 34.1 µmol / l (2 mg / dl) was in the group EISC 45.8%, in the group PTC - 64.5%, in the group PTAES - 63.9 % (p = 0.257); a month later, these figures were 11.7%, respectively; 12.5% and 17.9% (Fig. 5).

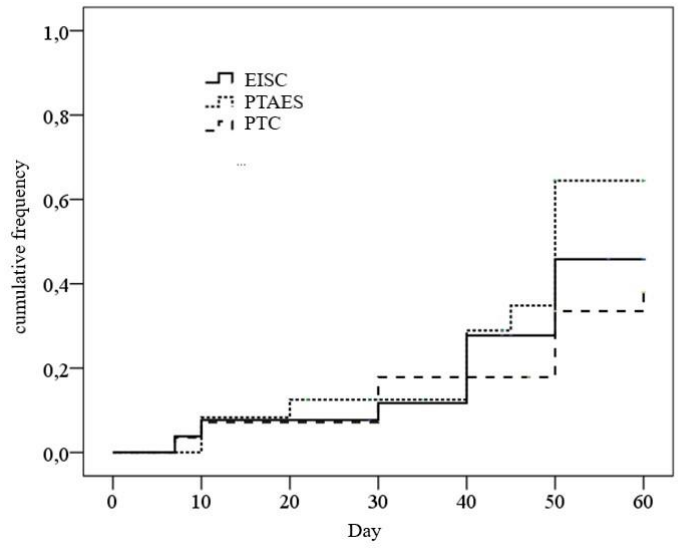

Figure 5. Cumulative frequency of bilirubin reduction to 34.2 µmol/l (2 mg / dl) during the observation period in groups

The decrease in bilirubin to 85.5 μmol / l (5 mg / dL) was faster. Thus, after 10 days the cumulative percentage of such patients in the groups exceeded 50.0%: in the group EISC 58.3%, in the group PTC - 63.6%, in the group PTAES - 57.7% (p = 0.26); a month later, these figures were 83.3%, respectively; 77.3% and 80.8%, after two months, respectively, 91.7%, 86.4 and 100% (p = 0.80, Fig. 6).

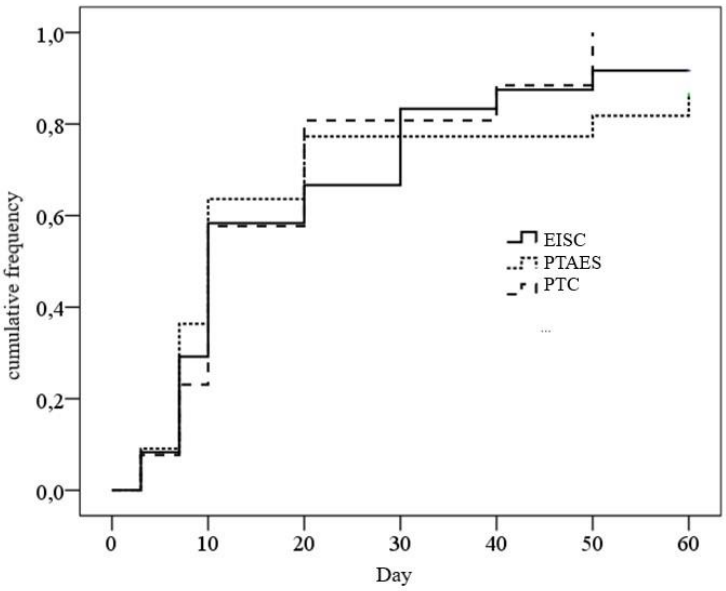

Figure 6. Cumulative frequency of bilirubin reduction to 85.5 μmol / l (5 mg / dl) during the observation period in groups

Discussion

Mechanical jaundice requires restoration of bile outflow. At high (hilar) blocks of biliary tracts two fundamentally different approaches are offered: antegrade and retrograde. Given the advantages and disadvantages of these approaches, the vector of their application is inclined in favor of antegrade techniques. This approach in patients with locally advanced hilar cholangiocarcinoma is recommended by a number of guidelines [6 - 8] because percutaneous intervention is associated with reduced time to therapeutic reduction of bilirubin, fewer infectious complications and repeated drainage procedures. [16 - 19].

There are few works that would determine the dynamics of bilirubin reduction depending on the applied method of bile duct decompression, and in addition, they evaluate different endpoints for the clinical success of the procedure (level and duration of bilirubin reduction). Thornton RH et al. considered the clinical success of the procedure to reduce the level of total bilirubin in the blood serum to 1 mg / dl (17.1 mmol / l), which according to their data was achieved by only 31% of patients with percutaneous transhepatic biliary drainage in 100 days [10] success was attributed to a decrease in serum bilirubin> 20% within 7 days after drainage, compared with the level of bilirubin before the procedure [20, 21]. In

the study of Jang SI et al. the endpoint was considered to be a decrease in bilirubin level of less than 50% during the month compared to the pre-procedure level [22]; other authors also used this indicator, but within two weeks after re-installation of the stent [23, 24]. Reasonable, in terms of the appointment of chemotherapy to study the dynamics of reducing the content of bilirubin in the serum to values safe for the appointment of a particular chemotherapy regimen - 2 or 5 mg / dL (34.2 or 85.5 mmol / l). Levy J.L. et al. determined the probability of achieving these target values of bilirubin within 90 days after percutaneous drainage / stenting and found that even in patients whose bilirubin level before drainage was within the highest quartile (19.8-37.4 mg / l), the average time to reaching a value of 5 mg / dL was only 40 days and among patients with baseline bilirubin> 2 mg / dL), the mean time to reach 2 mg / dL was 43 days [5]. In this paper, the assessment of the achievement of target points depending on the quartiles of the values of pre-procedural bilirubin and did not track the dynamics of the average values of bilirubin during the post-procedure period. In this work, the assessment of the achievement of target points depending on the quartiles of the values of pre-procedural bilirubin and did not track the dynamics of the average values of bilirubin during the post-procedure period. Although the authors used both percutaneous drainage and stenting in patients with proximal and distal stenosis, a comparative analysis of bilirubin dynamics in these subgroups is not presented.

We conducted a comparative evaluation of three variants of the antegrade approach: percutaneous transhepatic drainage, external-internal suprapapillary drainage and percutaneous transhepatic stenting of the bile ducts in patients with proximal (hilar) stenosis and mechanical jaundice.

The technical success of minimally invasive procedures, which was determined in the case of placement of the drainage tube in the biliary ducts in groups, was 100%.

In all groups, there was a decrease in mean bilirubin levels with increasing duration of the procedure. In all control terms, the average values of bilirubin did not differ statistically between groups, all $p > 0.05$. There were also no statistical differences between groups in the percentage reduction in mean bilirubin values in the control terms of the study relative to baseline levels, all $p > 0.05$.

It is noteworthy that in all groups the greatest rate of decrease in bilirubin was observed during the first 10 days (about 60.0%). From the 10th to the 60th day, the decrease in bilirubin levels occurred by approximately 20% from baseline.

According to regression analysis in all groups, the decrease in the percentage of bilirubin in each of the study periods did not depend on baseline bilirubin values (i.e., the

percentage decrease was approximately the same at high and low bilirubin values) so the control values were achieved faster at lower absolute bilirubin values. The cumulative percentage of patients in whom the level of bilirubin on the 60th day of the study reached 34.1 μmol / l (2 mg / dl) was in the group EITS 45.8%, in the group PTC - 64.5%, in the group PTAES - 63.9 % (p = 0.257); a month later, these figures were respectively 11.7%; 12.5% and 17.9%.

The decrease in bilirubin to 85.5 μmol / l (5 mg / dL) was faster. Thus, after 10 days the cumulative percentage of such patients in the groups exceeded 50.0%: in the group EISC 58.3%, in the group PTC - 63.6%, in the group PTAES- 57.7% (p = 0.257); a month later, these figures were 83.3%, respectively; 77.3% and 80.8%, after two months 91.7%, 86.4 and 100%, respectively (p = 0.802).

Therefore, our transcutaneous drainage / stenting methods effectively reduce serum bilirubin in patients with mechanical jaundice due to hilar organic block and do not have any statistically significant differences in the dynamics of bilirubin during the observation period.

Conclusions. The methods of transcutaneous bile ducts drainage/stenting effectively reduce the level of total bilirubin in patients with obstructive jaundice due to hilar stenosis caused by tumor and have no statistically significant differences in the dynamics of bilirubin level within two months of observation.

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