

EFFECTIVENESS OF DIFFERENT METHODS OF SURGICAL TREATMENT OF DIABETIC MACULOPATHY IN PATIENTS WITH TYPE 2 DIABETES**Yuliia Panchenko***PhD, Candidate of Medical Sciences**Kyiv Clinical Ophthalmology Hospital "Eye Microsurgery Center", Kyiv, Ukraine**Medical center "LASER Plus", Lviv, Ukraine*

Purpose. To study the effectiveness of different technologies of diabetic maculopathy (DMP) surgical treatment in patients with type 2 diabetes (T2D).

Method. 313 patients with T2D (313 eyes), with DMP and primary (group 1; n=40), moderate or severe non-proliferative diabetic retinopathy (NPDR; group 2; n=92), and proliferative diabetic retinopathy (PDR; group 3; n=181) were observed. The severity stages of both diabetic retinopathy (DRP) and DMP was determined according to the International Clinical Severity Scale of the American Academy of Ophthalmology (2002). The patients received four types of surgical treatment: 78 patients underwent three-port closed subtotal vitrectomy (CSV); 85 patients besides vitrectomy additionally underwent inner limiting membrane (ILM) peeling in the macular region; 81 patients underwent panretinal laser coagulation (PRLC) of the retina additionally to CSV and ILM peeling, and 69 patients additionally to all these interventions underwent cataract phacoemulsification (PHACO). The Statistica 10 program (StatSoft, Inc., USA) was used for statistical processing of the obtained data.

Result. The effectiveness of DMP surgical treatment amounted to 70.3 %; relapses occurred in 23.0 % of cases at the 1st month of follow-up, at the 3rd month — in 18.2 %, at the 6th month — in 10.2 % and after 1 year — in 24.9 % of cases. The effectiveness of the applied methods was as follows: CSV – 67.9 %, CSV + ILM peeling – 72.9 %, CSV + ILM peeling + PRLC – 71.6 %, CSV + ILM peeling + PRLC + PHACO – 68.1 %. These differences were not statistically significant (p=0.87). The relapse rate at different follow-up periods did not differ significantly in terms of treatment methods; only after 1 month of the follow-up the patients who underwent combined methods of surgical treatment (CSV with ILM peeling, PRLC with ILM peeling, PRLC with PHACO) experienced the relapses more frequently – 31.9 % (p=0.025). After CSV only, as well as after the combined application of all surgical interventions (CSV, ILM peeling, PRLC, PHACO) all the relapses were early, and the majority of them (77.3 and 80.0 % respectively) were persistent. In other variants of surgical intervention the majority of relapses (91-96 %) were determined as the early persistent and late ones. The effectiveness of surgical treatment has been reducing by retinopathy severity and amounts to 72.5 % in primary NPDR; to 77.2 % in moderate and severe NPDR, and to 66.3 % in PDR. The patients with PDR demonstrated both a higher relapse rate (33.7 %) and a higher relapse severity (a number of late relapses in patients in group 3 was 2.3 times greater than in the patients of groups 1 and 2; p=0.001).

Conclusion. The conducted studies have demonstrated high effectiveness of all methods which in a greater degree depended on the retinopathy severity, and were the least effective in PDR.

Key words: diabetic maculopathy, type 2 diabetes, surgical treatment, technologies, effectiveness.

The development of diabetic retinopathy (DRP) and diabetic maculopathy (DMP) is the main cause of disability due to the central vision impairment in type 2 diabetes (T2D) [1-3]. The patients with T2D demonstrate the signs of DRP in 10-15 years, and after the period of 30 years 90 % of diabetic patients have this vision impairment [4]. According to various authors' data, a DMP development is observed in 3-38 % of patients with non-proliferative DRP, in 20-63 % of patients with pre-proliferative DRP, and this number increases to over 70 % in patients with proliferative DRP [5].

DMP is manifested through microaneurysms, intraretinal microvascular abnormalities (IRMA), solid exudates, ischemia and posterior exfoliation of the vitreous body in the macula, and macular edema [1-3]. The changes in the vitreous body and posterior hyaloid membrane (PHM) are very important. The changes in PHM impair retinal metabolism, and cause and maintain macular edema. An incomplete self-detachment of the vitreous body can also form the tangential macular tractions, which explains the DMP

resistance to laser coagulation, intravitreal corticosteroids injections and anti-VEGF drugs [3, 5]. The vitreomacular traction (VMT) syndrome can be accompanied by DMP, and in this case an extension of the traction causes a vitreomacular separation and cystoid changes [6].

The surgical treatment, namely vitrectomy with endolasercoagulation of the retina, tamponade of the vitreous cavity, removal of the posterior hyaloid membrane and, if needed, with internal limiting membrane peeling (ILM) of the retina, is used for the treatment of DMP in forms which are more severe and more resistant to conservative and laser methods, as well as to anti-VEGF therapy [1, 3, 7]. Vitrectomy is an effective procedure for DMP treatment, and the effect can be improved by an additional ILM peeling, without increasing the frequency of intra- and postoperative complications [8]. Vitrectomy has been shown to lead to structural and functional improvement of certain regions of the retina, including the macula, however, central vision improvement is not much better than when laser intervention is used [9]. For example, visual

acuity in patients with nontractional macular edema who underwent pars plana vitrectomy with and without ILM peeling was not significantly different [10]. Pars plana vitrectomy combined with cataract surgery in patients with T2D has achieved good results without a significant increased risk of visual acuity decrement or other complications, which indicates a high effectiveness of the combined surgical intervention [11].

Purpose of the study – to study the effectiveness of different variants of vitreoretinal interventions by the number of DMP relapses in patients with T2D.

Materials and methods of the study. 313 patients with T2D (313 eyes), with DMP and primary (group 1; n=40), moderate or severe non-proliferative diabetic retinopathy (NPDR; group 2; n=92), and proliferative diabetic retinopathy (PDR; group 3; n=181) were observed by us.

All the patients underwent the conventional ophthalmic examinations, including visometry, Humphrey visual field testing, refractometry, tonometry, biomicroscopy, gonioscopy, ophthalmoscopy with a Volk Super/Field (NC USA) aspheric lens and a Goldmann three-mirror contact lens. The patients underwent a spectral domain optical coherence tomography (OCT) on Optopoltechnology device, SOCT, Copernicus REVO (Retina3D protocol, RetinaRaster) and OCT using Angio mode (RetinaAngio protocol, wide 6x6 mm). The fundus of the eye was also examined with fundus camera with photographing in 7 standard fields according to the modified Airlie House ETDRS system of clinical features classification.

The severity stage of DRP and DMP was determined according to the International Clinical Diabetic Retinopathy and Diabetic Maculopathy Severity Scale of the American Academy of Ophthalmology (2002). [12].

The progressive reduction of visual acuity, visual field changes in the central and paracentral departments, changes in quality of vision due to NPDR with refractory macular edema or macular edema with tangential tractions, which appeared due to incomplete detachment of the posterior hyaloid membrane of the vitreous body, as well as due to PDR with refractory macular edema, epiretinal membranes, and tangential and axial retinal tractions of the retina and the threat for tractional retina detachment, and also hemophthalmos, preretinal and subhyaloid hemorrhages were the indications for a surgical intervention.

In this study the patients received four types of surgical treatment. 78 patients underwent a three-port closed subtotal vitrectomy (CSV) 25+ on the Constellation Vision System device (Alcon, USA) using the Constellation TOTALPLUS cassette, combined 7500CPM, 25+ caliber (Alcon, USA). An extrusion line was used for posterior exfoliation of the vitreous body, posterior hyaloid and epiretinal membranes were removed with a vitreotome or vitreal forceps. Tangential and axial retinal tractions were removed as well. Vitrectomy of the extreme peripheral retina was performed by means of sclerocompression.

20 % gas-air mixture C3F8 was injected into the vitreous cavity. The trocars were removed and the ports were sealed. Besides vitrectomy 85 patients additionally underwent ILM peeling in the macular region 2.5-3.5 mm in diameter with a preliminary injection of MembraneBlue dye into the vitreous cavity for clear ILM visualization. Besides CSV and ILM peeling 81 patients additionally underwent panretinal laser coagulation (PRLC) of the retina with 25-gauge endolaser probe. Additionally to all these interventions 69 patients underwent cataract phacoemulsification (PHACO). All patients were examined in 1, 3, 6 months and in 1 year after the surgery. The relapse rate of the surgical treatment was determined by the presence of DMP signs (microhemorrhage, IRMA, solid exudates, etc.), and macular edema.

The Statistica 10 program (StatSoft, Inc., USA) was used for statistical processing of the obtained data. A distribution of variation series that differs from normal one ($p < 0.05$) was determined after conducting Kolmogorov-Smirnov, Anderson-Darling and Pearson's chi-square (χ^2) tests. Thereby, we used the median (Me) and the first and third quartiles (Q1; Q3) of the variation series for the descriptive statistics of quantitative data. The cross-tabulation and nonparametric Pearson criterion χ^2 were used to compare the categorical variables. The value $p < 0.05$ was considered plausible in all cases of statistical evaluation.

Results and their discussion

The maximum corrected visual acuity before the surgery ranged from 0.01 to 0.9 and amounted in average to 0.174 ± 0.012 . The central, paracentral or absolute scotomas were found in 97 eyes (31.09 %). The patients prior to surgery have demonstrated the following DMP signs: microaneurysms and microhemorrhages in the macular region, intraretinal microvascular abnormalities (IRMA), depositions of solid exudates, and macular edema of different levels of manifestation with cystic cavities. The mean retinal thickness ranged from 195 μm to 880 μm and averaged $358.09 \pm 6.96 \mu\text{m}$.

All the surgeries were fully performed. The intraoperative complications included microhemorrhages after ILM removal in 6-7 % of cases, which resolved without additional treatment during the first two days after the surgery. Partial hemophthalmos has determined in 2-3 % of cases by the time vitrectomy was completed. Its distribution was blocked by the tamponade of the vitreous cavity with perfluororganic compounds (DK-Line) and by increasing the irrigation parameters to 40.0 mm Hg. Upon bleeding control perfluororganic compounds were eliminated and irrigation parameters were normalized to 25.0 mm Hg. In all cases, hemophthalmos regressed without additional treatment within 2-3 days.

The relapse rate overall amounted to 29.7 % (93 eyes) one year after surgery, so the effectiveness of DMP surgical treatment amounted to 70.3 %. The relapses in postoperative period (Fig.1) occurred in 23.0 % (72 eyes) at the 1st month of follow-up, at the

3rd month – in 18.2 % (57 eyes), at the 6th month – in 10.2 % (32 eyes) and in 24.9 % (78 eyes) after one year

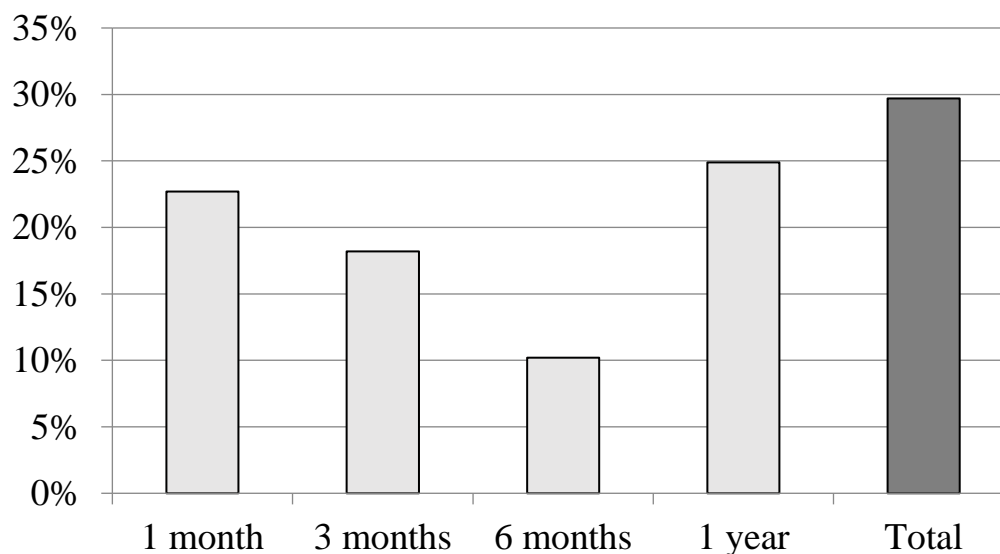


Fig. 1. DMP relapse rate within one year after surgical treatment (total) and during follow-up period (in 1, 3, 6 months and 1 year).

The overall relapse rate of DMP throughout all observation in terms of surgical treatment method is presented in Table 1 and (for demonstration of negative findings) in Figure 2.

Table 1
DISTRIBUTION OF PATIENTS BY PRESENCE AND ABSENCE OF DMP RELAPSES IN TERMS OF TREATMENT METHODS (BY ALL GROUPS OF PATIENTS)

Relapses	CSV	CSV+ILM peeling	CSV+ILM peeling+PRLC	CSV+ILM peeling+PRLC+PHACO	χ^2	p
	n=78	n=85	n=81	n=69		
presence	25 32.1%	23 27.1%	23 28.4%	22 31.9%	0.714	0.870
absence	53 67.9%	62 72.9%	58 71.6%	47 68.1%		

Notes: n – total number of patients with the applied method of treatment; χ^2 – Pearson criterion; p – probability of differences in comparisons between groups.

The incidence of complications out of total number of patients who underwent CSV amounted to 32.1% (25 eyes), CSV and ILM peeling – 27.1% (23 eyes), CSV, ILM peeling and PRLC – 28.4 % (23 eyes) and CSV, ILM peeling, PRLC and PHACO – 31,9% (22 eyes). The effectiveness of the applied methods

respectively amounted to: CSV – 67.9 %, CSV + ILM peeling – 72.9 %, CSV + ILM peeling + PRLC – 71.6 %, CSV + ILM peeling + PRLC + PHACO – 68.1 %. These differences, however, were not statistically significant (p=0.87).

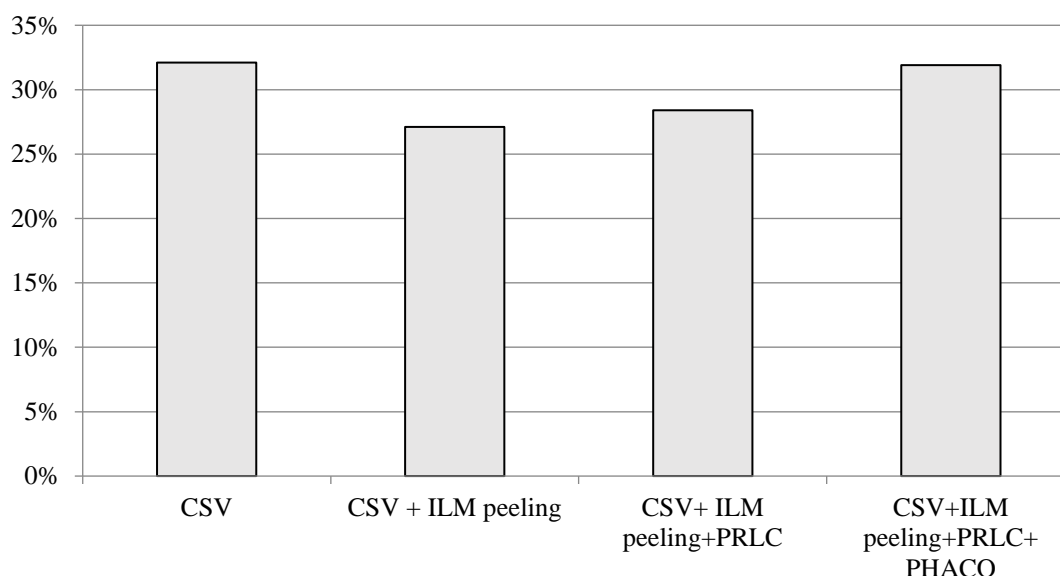


Fig. 2. DMP relapse rate in terms of the surgical treatment method within one year after surgical treatment; $\chi^2=0.714$; $p=0.870$

The relapse rate in terms of treatment methods at different follow-up periods (Table 2) did not differ significantly from the general trend (see Fig. 1). The relapses were more frequent solely after 1 month after surgery in those patients who underwent the maximum amount of different surgeries (CSV, ILM peeling,

PRLC, and PHACO): 31.9 % ($p=0.025$). The minimum number of relapses was observed after CSV, ILM peeling and PRLC after 1 and 3 months follow-up period (14.8 % each); relapse rates by treatment methods were not generally different 6 months and 1 year after surgery.

Table 2

DMP RELAPSE RATE BY TREATMENT METHODS IN FOLLOW-UP CONTROL (FOR ALL GROUPS OF PATIENTS)

Follow-up period	CSV	CSV+ILM peeling	CSV+ILM peeling+PRLC	CSV+ILM peeling+PRLC+PHACO	χ^2	P
1 month	n=78	n=85	n=81	n=69	9.367	0.025
	22 28.2%	15 17.6%	12 14.8%	22 31.9%		
3 months	n=78	n=85	n=81	n=69	1.276	0.735
	15 19.2%	15 17.6%	12 14.8%	15 21.7%		
6 months	n=78	n=85	n=81	n=65	0.038	0.998
	8 10.3%	9 10.6%	8 9.9%	7 10.8%		
1 year	n=78	n=85	n=78	n=65	0.179	0.981
	19 24.4%	21 24.7%	21 26.9%	17 26.2%		

Notes: n – total number of patients with the applied method of treatment; χ^2 – Pearson criterion; p – probability of differences in comparisons between groups.

Late relapses occurring 6 months and 1 year after surgery are considered to be the most dangerous ones, as they are persistent and can no longer be corrected by further surgeries [1-3]. Early relapses tend to disappear, i.e. they are transient.

The distribution of DMP relapses after surgical treatment depending on their occurrence was observed

in the our study (Table 3). All relapses were divided into three types: early transient – those that occurred at 1-3 months and subsequently disappeared; early persistent – those that occurred at 1-3 months and then remained for 6 months and 1 year; late – those that occurred after 6 months and 1 year.

Table 3

DMP RELAPSE RATE BY TREATMENT METHODS IN TERMS OF THEIR PERIOD OF OCCURRENCE

Relapses by type	CSV	CSV+ILM peeling	CSV+ILM peeling+PRLC	CSV+ILM peeling+PRLC+PHACO	χ^2	p
	n=78	n=85	n=81	n=69		
Early transient	5 6.4%	2 2.4%	1 1.2%	5 7.3%	5.081	0.166
Early persistent	20 25.6%	14 16.5%	13 16.1%	17 24.6%		
Late	0 0.0%	7 8.2%	9 11.1%	0 0.0%	15.639	0.001
χ^2 ; p	$\chi^2=22.091$; p=0.001					

Notes: n – total number of patients with the applied method of treatment; χ^2 – Pearson criterion; p – probability of differences in comparisons between groups.

Such type of analysis demonstrated some differences between the applied methods of DMP surgical treatment. Thus, the early persistent relapses were the most frequent ones, which depending on different methods of treatment ranged from 16.1 % to 25.6 %. The patients who underwent CSV and combination of CSV, ILM peeling, PRLC and PHACO did not have any late complications. In the latter case, the difference between the groups was statistically significant (p=0.001).

Thus, after CVS and also when the combination of CSV, ILM peeling, PRLC and PHACO was used, all

relapses experienced by the patients were early, the majority of them (77.3 and 80.0 % respectively) were persistent. After CSV with ILM peeling and also when the combination of CSV, ILM peeling and PRLC was used, the majority of relapses were classified as early persistent and late ones (91.3 % and 95.7 % respectively), and thus had the unfavorable character.

This study included the patients with DMP, which occurred due to DRP of different severity. So, we have separately analyzed the distribution of relapse rate by groups of patients (Table 4 and Fig. 3).

Table 4

DISTRIBUTION OF PATIENTS BY THE PRESENCE AND ABSENCE OF DMP RELAPSES BY GROUPS OF PATIENTS (BY ALL TREATMENT METHODS)

Relapses	Group 1	Group 2	Group 3	χ^2	p
	n=40	n=92	n=181		
presence	11 27.5%	21 22.8%	61 33.7%	3.433	0.180
absence	29 72.5%	71 77.2%	120 66.3%		

Notes: n – total number of patients in groups; χ^2 – Pearson criterion; p – probability of differences in comparisons between groups.

The relapse rate within 1 year amounted to: group 1 – 27.5 % (11 eyes), group 2 – 22.8 % (21 eyes), and group 3 – 33.7 % (61 eyes). This indicated that the relapse rate depended on the severity of DRP as more relapses were observed in PDR. However, it should be noted that the overall analysis did not show any statistically significant difference (p=0.180), so more

thorough analysis was required. Therefore, in general, the effectiveness of DMP surgical treatment amounts to 72.5 % in primary NPDR; 77.2 % in moderate and severe NPDR, and 66.3 % in PDR. In our opinion, such result could not be considered the final one and required a more detailed research.

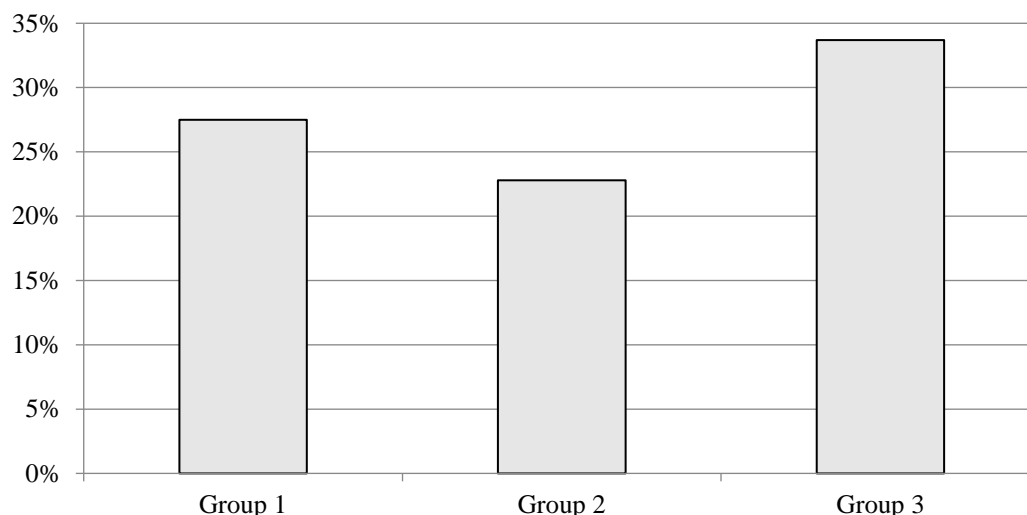


Fig. 3. DMP relapse rate within 1 year after surgical treatment by groups of patients; $\chi^2=3.433$; $p=0.18$

Thus, the relapse rate analysis in groups of patients (Table 5) by the follow-up periods has indicated that group 3 is characterized by maximum relapse number (32.2 %), which was statistically significant after 1 year at the level of $p=0.008$.

Table 5

DMP RELAPSE RATE BY GROUPS OF PATIENTS (BY ALL TREATMENT METHODS)

Follow-up period	Group 1	Group 2	Group 3	χ^2	p
1 month	n=40	n=92	n=181	0.467	0.792
	9 22.5%	19 20.7%	44 24.3%		
3 months	n=40	n=92	n=181	4.363	0.113
	5 12.5%	12 13.0%	40 22.1%		
6 months	n=40	n=92	n=177	5.467	0.065
	0 0.0%	10 10.9%	22 12.4%		
1 year	n=40	n=92	n=174	9.537	0.008
	7 17.5%	15 16.3%	56 32.2%		

Notes: n – total number of patients in groups; χ^2 – Pearson criterion; p – probability of differences in comparisons between groups.

The relapse rate in group 3 was 1.7 times bigger than in of both groups 1 and 2 after 3 months. On the whole, the patients of group 1 did not experience any relapses after 6 months. The relapse rate in group 3 again was 1.8 and 2.0 times higher than in groups 1 and 2 respectively after 1 year ($p=0.008$).

The distribution by relapse type was as follows

(Table 6). Early persistent complications were prevalent in all groups, ranging from 54.5 % in group 1 to 72.1 % in group 3 (% out of the number of complications in the group). However, the early transient complications were more common among the other complications in the 1st group (36.4 %), while the late complications — in the 3rd group (21.3 %).

DMP RELAPSE RATE BY GROUPS OF PATIENTS IN TERMS OF THEIR PERIOD OF OCCURRENCE

Relapses by type	Group 1	Group 2	Group 3	χ^2	P
	n=11	n=21	n=61		
Early transient	4 36.4%	5 23.8%	4 6.6%	5.531	0.063
Early persistent	6 54.5%	14 66.7%	44 72.1%	3.936	0.140
Late	1 9.1%	2 9.5%	13 21.3%	15.639	0.001
χ^2 ; p	$\chi^2=9.974$; p=0.041				

Notes: n – total number of patients in groups; χ^2 – Pearson criterion; p – probability of differences in comparisons between groups.

Thus, group 3 was not only characterized by the big number of relapses but by their severity as well, and absolute majority of such cases (93.4%) consisted of early persistent and late relapses. The number of late relapses in patients of group 3 was 2.3 times bigger than in groups 1 and 2 (p=0.001). Therefore, the patients with PDR demonstrated both a higher relapse rate and a greater relapse severity in DMP surgical treatment, and, thus, the effectiveness of surgical interventions in DMP treatment was lower in cases with PDR, which was especially true for persistent and late relapses.

The analysis of how the treatment methods influence the relapse rate of DMP in groups of patients for all follow-up periods (after 1, 3, 6 months and 1 year) indicated that the difference in number of DMP relapses in different methods of surgical treatment was not statistically significant (p>0.7) for any of the follow-up periods. This again confirms the similar effectiveness of DMP treatment methods that have been applied. Instead, the effectiveness of DMP treatment clearly depended on the severity of DRP. Thus, the number of relapses in patients of group 1 during the follow-up period of all treatment methods ranged from 0 % to 16.7 %, in patients of group 2 – from 13.3 % to 37.5 %, whereas in patients of group 3 – from 50.0 % to 86.7 %. Hence, the effectiveness of DMP surgical treatment clearly depends on primary severity of DRP, as it is the most severe in cases with PDR.

Conclusions

1. The effectiveness of DMP surgical treatment amounted to 70.3 %; relapses occurred in 23.0 % of cases at the 1st month of follow-up, at the 3rd month — in 18.2 %, at the 6th month — in 10.2 % and after 1 year — in 24.9 % of cases.

2. The effectiveness of modern surgical methods of DMP treatment of the patients with T2D amounted to: CSV – 67.9 %, CSV + ILM peeling – 72.9 %, CSV + ILM peeling + PRLC – 71.6 %, CSV + ILM peeling + PRLC + PHACO – 68.1 %. These differences were not statistically significant (p=0.87).

3. The relapse rate in treatment methods at different follow-up periods did not differ significantly.

The patients who underwent combined methods of surgical treatment (CSV with ILM peeling, PRLC with ILM peeling, PRLC with PHACO) experienced more frequent relapses after 1 month – 31.9 % (p=0.025).

3. After CSV only, as well as after the combined application of all surgical interventions (CSV, ILM peeling, PRLC, PHACO) all the relapses were early, and the majority of them (77.3 and 80.0 % respectively) were persistent. In other variants of surgical intervention the majority of relapses (91-96 %) were determined as the early persistent and late ones.

4. The effectiveness of DMP surgical treatment has been reducing by the retinopathy progression and amounts to 72.5 % in primary NPDR; 77.2 % in moderate and severe NPDR and 66.3% in PDR. The patients with PDR demonstrated both a higher relapse rate (33.7 %) and a higher relapse severity (a number of late relapses in patients in group 3 was 2.3 times greater than in the patients of groups 1 and 2; p=0.001).

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