ORIGINAL ARTICLE

Pars Plana Vitrectomy and Combination Therapy Pars Plana Vitrectomy, Intravitreal Triamcionolone Acetonide and Macular Lasercoagulation – One Year Results

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SUMMARY

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Purpose. To compare anatomic and functional results of pars plana vitrectomy with MLI peeling (group PPV) and pars plana vitrectomy with MLI peeling, intravitreal triamcinolon acetonide 4 mg and macular lasercoagulation (group PPV + TRIAM) in eyes with diffuse diabetic macular edema (DEM).
Methods: In the group PPV eyes underwent PPV with MLI peeling and in the group PPV + TRIAM, PPV with MLI peeling, intravitreal triamcinolon acetonide 4 mg was performed at the end of surgery and macular lasercoagulation 3 weeks after surgery. Best corrected visual acuity (BCVA), central macular thickness (CMT) and macular volume were recorded before, 1, 3, 6 and 12 months after vitrectomy.
Results: Sixty – eight eyes from 59 subjects with DEM non responsive to lasercoagulation or with vitreomacular traction were enrolled, the group PPV 35 eyes and the group PPV + TRIAM 33 eyes. In the group PPV before and 1, 3, 6 a 12 months after surgery mean BCVA were 0,22; 0,21; 0,28; 0,32; 0,30, mean CMT were 497,69 µm; 400,89 µm; 356,46 µm; 346,89 µm; 319,49 µm and mean macular volume were 11,48 mm3; 9,82 mm3; 9,28 mm3; 9,07 mm3, 8,83 mm3. In the group PPV + TRIAM mean BCVA were 0,18; 0,16; 0,23; 0,26; 0,26, mean CMT were 447,82 µm; 276,03 µm; 266,27 µm; 268,36 µm; 251,15 µm, mean macular volume were 10,71 mm3; 8,03 mm3; 8,28 mm3; 7,96 mm3; 7,66 mm3. In both groups statistical significant improvement in BCVA were observed from month 3 ($p = 0.0013$), in CMT and macular volume from month 1 (< 0.001). To compare both groups, in the group PPV + TRIAM changes in CMT and macular volume in month 1 after combination therapy from baseline were statistical significant, but without statistical significant, change in BCVA ($p = 0.229$). The major complications after surgery were an elevation of intraocular pressure and cataract surgery, more often in the group PPV + TRIAM ($p = 0.153$, $p = 0.056$). Conclusion: Both surgical technics are effective in the treatment of DEM. Combination therapy PPV, triamcinolon acetonide 4mg and macular lasercoagulation is associated with higher number of complications after surgery (elevation of intraocular pressure and cataract surgery).

Key words: diabetic macular edema, pars plana vitrectomy, combination therapy

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Diabetes mellitus is a serious health problem, and its prevalence is continuing to rise. An ageing population, changes in dietary habits and an increase in obesity have brought about a situation in which an ever increasing number of individuals are afflicted by this disorder and the complications connected therewith.
Diabetic retinopathy is one of the most widely discussed microvascular complications of DM disorder. In the age group of 25-74 years it is the most frequent cause of blindness in developed countries. The standard treatment of diabetic retinopathy to date is lasercoagulation. In the Early Treatment Diabetic Retinopathy Study (ETDRS) (8) it was confirmed that lasercoagulation in the treatment of diabetic macular edema (DME) reduces medium-severe loss of central visual acuity (CVA) by 50%, but that even despite this intensive treatment a deterioration of CVA occurs in certain patients. One of the options for treatment of patients with DME, in particular diffuse DME, is pars plana vitrectomy (PPV). It is envisaged that a relaxation of all tractional forces on the retina and an improvement of oxygenation of the retina after PPV can reduce changing of the retina (29). Corticosteroids applied to the vitreous cavity may cause a reduction of swelling of the retina, and depending on the extent of macular ischemia also lead to an improvement of CVA (15). PPV is sometimes used for visualisation of the vitreous area, assists the complete removal thereof, alleviates peeling of the internal limit membrane (membrana limitans interna - MLI) and in the postoperative period is used for its anti-inflammatory and anti-edematous effect. In ophthalmology the most commonly used substance is

triamcionolone acetonide (TRIAM (15).
The aim of this prospective study on eyes with DME which do not respond to lasercoagulation or with a presence of vitreomacular traction is to compare the functional and anatomical results of PPV operations with peeling of MLI and PPV with peeling of MLI supplemented with application of TRIAM at the end of the operation and lasercoagulation of the macula 3 weeks after the operation.

MATERIAL AND METHOD

Eyes were included in the prospective non-randomised observation after the following criteria: length of duration of DME less than 2 years (24 months); period of observation minimum 12 months and adherence to regular check-ups according to ordering; HbA1c less than 10% by DCCT method for last year before operation; detailed internal examination with data on present hypertension, dyslipidemia and proteinuria; CVA less than 0.6 on Snellen optotypes; finding of DME with vitreomacular traction confirmed by OCT or DME not responding to lasercoagulation; central macular thickness (CMT) > 300 μm on OCT; PPV without lens removing in one session; clear optical media in 1st, 3rd, 6th and 12th month after operation in order to enable OCT examination (absence of blood, exudate, silicon oil or gas in vitreous cavity). The criteria for excluding eyes from the observation were as follows: lasercoagulation of macula less than 3 months before operation, panretinal lasercoagulation less than 4 months before operation, intravitreal application of corticosteroids or vascular endothelial growth factor (VEGF) inhibitors less than 3 months before operation, previous PPV, other eye operation less than 6 months before operation (e.g. operation on lens or trabeculectomy), unclear optical media in postoperative period.
In the PPV group, PPV was used on all eyes with MLI peeling. Lasercoagulation was possible at the earliest 3 months after the operation. In the PPV + TRIAM group all eyes were treated with PPV with MLI peeling and application of TRIAM 4 mg into the vitreous cavity at the end of the operation, and lasercoagulation of the macula 3 weeks after the operation.
After the operation the eyes were examined in the 1st, 3rd, 6th and 12th month in both groups. At each check-up the following examinations were performed: CVA, CMT and macular volume on OCT (Stratus 3.0 Zeiss Humphrey, San Leonardo, California, USA), intraocular pressure (IOP) was measured and the occurrence of postoperative complications was observed. Central visual acuity was examined on Snellen's optotypes and presented in a decimal score. We considered an improvement by 2 or more rows of Snellen's optotypes to constitute an improvement of CVA, a deterioration by 2 or more rows of Snellen's optotypes to represent a deterioration of CVA and ± 1 row of Snellen's optotypes to represent stabilisation of CVA.
In the postoperative period early complications which appeared within 1 month of the operation and later complications were observed.
Additional lasercoagulation in the PPV group was possible according to the decision of the ophthalmologist after 3 months following the operation. In the PPV + TRIAM group, additional lasercoagulation in the case of persistent DME was possible 3 months after lasercoagulation performed 3 weeks after the operation. Intravitreal application of medicaments in the postoperative period was not possible for any patient.
For the statistical processing of data we used the Wilcoxon non-parametric signed-rank test. Fisher's exact test was used in determining the difference in the necessity for operation on the lens in the postoperative period between the PPV and PPV + TRIAM groups. We considered $p < 0.05$ to represent a statistically significant level. We measured the correlation between the individual observed parameters or change thereto using the Pearson product-moment correlation coefficient.

RESULTS

The prospective non-randomised observation included 68 eyes in 59 patients, of whom 27 were men and 32 women. In the PPV group we observed 35 eyes in 28 patients, of whom 14 were men (50%) and 14 women (50%). In the PPV + TRIAM group we observed 33 eyes in 31 patients, of whom 13 were men (42%) and 18 women (58%). The average age of the patients included in the PPV group was 59.71 ± 10.0 years, from 37 to 80 years. In the PPV + TRIAM group the average age was 62.36 ± 6.39 years, from 52 to 76 years. The PPV group included 27 patients (96.43%) with type 2 DM and one female patient (3.57%) with type 1 DM. The average length of duration of DM at the time of the operation was 15.34 ± 9.44 years. The average HbA1c value before the operation was 8.40 ± 0.78% in this group. The PPV + TRIAM group included 29 patients (93.55%) with type 2 DM and two patients (6.45%) with type 1 DM. The average length of duration of DM at the time of the operation was 16.15 ± 8.73 years and the average HbA1c value before the operation was 8.33 ± 0.89%. In both groups the observation period was 12 months. The period of deterioration of CVA recorded subjectively by the patient was 12.97 ± 7.93 months in the PPV group and 14.94 ± 6.27 months in the PPV + TRIAM group (table 1).
In the PPV group NPDR was present in 28 eyes (80%) and PDR in 7 eyes (20%). In the PPV + TRIAM group NPDR was present in 30 eyes (90.91%) and PRD in three eyes (9.09%). In eyes with PDR only small neovascularisation was determined on the disc of the optic nerve (DON) without traction on the surrounding retina. Diabetic macular edema was present in all eyes in both groups. Vitreomacular traction was an indication for operation in the PPV group in 26 eyes (74.29%), and 28 eyes (84.45%) in the PPV + TRIAM group. Small vitreous bleeding was observed in 5 eyes (14.28%) in the PPV group and in one eye (3.03%) in the PPV + TRIAM group (table 2).

Table 1 Characteristics of examined groups of patients

	PPV		PPV + TRIAM	
	average	± SD	average	± SD
Age (years)	59.71	10.0	62.36	6.39
Duration of DM (years)	15.34	9.44	16.15	8,73
HbA1c (%)	8.40	0.78	8,33	0.89
Observation (months)	12	0	12	0
Deterioration of CVA (months)	12.97	7.93	14.94	6.27

All patients underwent standard 3-gate PPV. In the PPV group 23G PPV was performed on 14 eyes (40%) and in the PPV + TRIAM group on 30 eyes (90.91%). Before the operation a epiretinal membrane (ERM) was diagnosed in 12 eyes (34.29%) in the PPV group and 7 eyes (21.21%) in the PPV + TRIAM group. ERM was determined during the surgery in 17 eyes (48.57%) in the PPV group and 13 eyes (39.39%) in the PPV + TRIAM group. In 25 eyes (71.43%) in the PPV group and 29 eyes (87.88%) in the PPV + TRIAM group tamponade of the vitreous cavity was not required at the end of the operation. MLI peeling following prior colouring with trypan blue and cryocoagulation with sclerotomy at the end of the operation was performed on all eyes (table 3).

Table 2 Preoperative local finding

Name	PPV		PPV + TRIAM	
	N	%	N	%
Phakia	22	65.71	25	75.76
Pseudophakia	13	37.14	8	24.24
Galucoma	2	5.71	3	9.09
NDPR	28	80	30	90.91
PDR	7	20	3	9.09
Lasercoagulation-f/m ~	31	88.57	31	93.94
Lasercoagulation - PRP	29	82.9	22	66.7
Vitreous haemorrhage	5	14.28	1	3.03

~ lasercoagulation focal/grid, PRP – panretinal photocoagulation

Table 3 Characteristics of operation procedures

Name	PPV		PPV + TRIAM	
	N	%	N	%
PPV				
20G	21	60	3	9.09
23G	14	40	30	90.91
ERM/Ablation	17	48.57	13	39.39
MLI peeling	35	100	33	100
No capsulectomy	12	34.29	8	24.24
Tamponade of vitreous cavity				
Infusion solution	25	71.43	29	87.88
Air	3	8.57	1	3.03
SF6 gas 7	7	20	3	9.09
C3F8 gas	0	0	0	0
Lasercoagulation				
Retinal rupture	1	2.86	0	0
PRP	16	45.71	8	24.24
Cryocoagulation				
Retinal Rupture	6	17.14	3	9.09
With sclerotomy	35	100	33	100

Table 4 Average values of central visual acuity

	Before operation	1st month	3rd month	6th month	12th mont
PPV	0.22	0.21	0.28	0.32	0.30
PPV + TRIAM	0.18	0.16	0.23	0.26	0.26

Central visual acuity

Average CVA in the 12th month after the operation in the PPV group was 0.30, compared with 0.26 in the PPV + TRIAM group. In the PPV group CVA improved by 2 or more rows in 10 eyes (28.57%), decreased by 2 or more rows in 2 eyes (5.72%) and stabilisation was attained in 23 eyes (65.71%). In the PPV + TRIAM group in the 12th month we observed an improvement of CVA by 2 or more rows in 7 eyes (21.21%), a decrease by 2 or more rows in 1 eye (3.03%) and stabilisation was attained in 25 eyes (75.76%) (table 4).

The average change of CVA in the PPV group in the 12th month was 0.11 (CI 95%; 0.05, 0.16, p = 0.0013), in the PPV + TRIAM group 0.08 (CI 95%; 0.03, 0.13, p < 0.001). No statistically significant difference in the observed value of CVA between the PPV and the PPV + TRIAM groups in the 12th month was confirmed, p = 0.375 (table 5, graph 1).

Central macular thickness

Average CMT before the operation in the PPV group was 497.69 ± 168.92 µm and in the PPV + TRIAM group 447.82 ± 119.53 µm (table 6). In the PPV group 20 of 35 eyes (57.14%) had CMT < 300 µm in the 12th month, in which 16 of 35 eyes (45.71%) had CMT < 250 µm. In a further 6 of the 35 eyes (17.14%) CMT was reduced by more than 20%. In the PPV +TRIAM group 30 of 33 eyes (90.90%) had central macular thickness < 300 µm in the 12th month, in which 16 of 33 eyes (48.48%) had CMT < 250 µm. In two eyes of 35 (5.71%) in the PPV group and two eyes of 33 (6.06%) in the PPV + TRIAM group CMT had increased in the 12th month by more than 20%, and this trend continues in the further months of observation. In the 12th month the average change of CMT in the PPV group was -178 µm (CI 95%; -50, -144 µm, p < 0.001) and in the PPV + TRIAM group -197 µm (CI 95%; -142, -252 µm, p < 0.001) (table 6,7 graph 2). In both groups a statistically significant reduction of CMT occurred (p < 0.001) in all the observed months following the operation, in which no more marked differences were recorded in the individual months between the groups, with the exception of the first month. In the first month after the operation, the reduction of CMT in the PPV + TRIAM group was found to be double that in the PPV group, which is caused by the use of TRIAM at the end of the operation (p = 0.002) (table 7, graph 2).

Macular volume

In the PPV group the average volume of the macula before the operation was 11.48 ± 2.39 mm3 and in the PPV

Table 5 Comparison of PPV group with PPV + TRIAM group. Average values of central visual acuity before operation up to 12th month

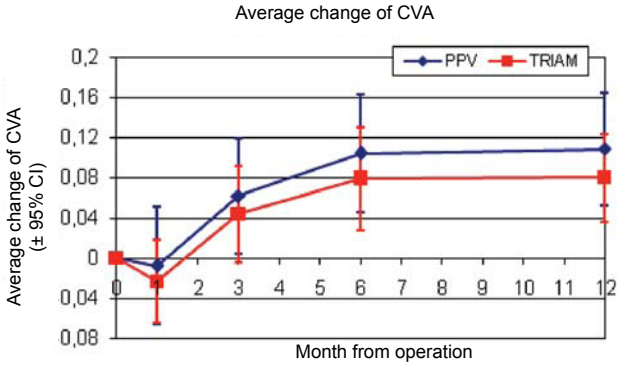
PPV v PPV + TRIAM	Before operation	1st month	3rd month	6th month	12th mont
PPV	0	-0.01	0.06	0.10	0.11
PPV + TRIAM	0	-0.02	0.04	0.08	0.08
	p-value	0.229	0.276	0.512	0.375

Table 6 Average values of central macular thickness (µm)

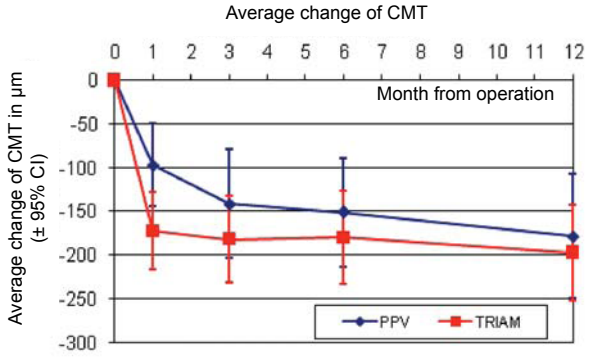
	Before operation	1st month	3rd month	6th month	12th mont
PPV	497.69	400.89	356.46	346.89	319.49
PPV + TRIAM	447.82	276.03	266.27	268.36	251.15

Table 7 Comparison of PPV group with PPV + TRIAM group. Average values of central macular thickness (µm) before operation up to 12th month

PPV v PPV + TRIAM	Before operation	1st month	3rd month	6th month	12th mont
PPV	0	-97	-141	-151	-178
PPV + TRIAM	0	-172	-182	-179	-197
	p-value	0.002	0.081	0.218	0.289



Graph 1 Average change of central visual acuity



Graph 2 Average change of central macular thickness (µm)

+ TRIAM group 10.71 ± 2.62 mm3. The average volume of the macula in the 12th month following the operation was reduced to 8.83 mm3 and 7.66 m3 respectively (table 8).

In the 12th month following the operation, the average change to the volume of the macula in the PPV group was -2.65 mm3 (CI 95%; -1.57, 3.73, $p < 0.001$). In the PPV + TRIAM group the average change to the volume of the macula in the 12th month was -3.05 mm3 (CI 95%; -2.18, -3.92 mm3, $p < 0.001$). In all the observed months in both groups there was a reduction of the volume of the macula ($p < 0.001$) without more marked differences in the individual months with the exception of the first month. In the first month following the operation we recorded a more marked reduction in the volume of the macular in comparison with the PPV group, which as in the case of CMT is caused by the use of TRIAM at the end of the operation ($p = 0.027$) (table 8, 9, graph 3).

On the graphs illustrating the relationships between the initial values – dependency of CVA on CMT – we can see that in the PPV group more eyes with a higher CMT value were included than in the PPV + TRIAM group. The occurrence of eyes with lower initial CVA values was approximately equal in both groups (graph 4, 5).

On the resulting graphs we can see the resulting shift towards lower CMT values and higher CVA values (graph 6, 7).

For a comparison of the dependency between the individual groups, we compared the initial values of CVA, CMT, macular volume and the change in the 12th month. We expressed the correlation using the Pearson product-moment correlation coefficient.

In the PPV group we demonstrated a statistical dependency between the initial CMT value and macular volume with a change in the 12th month ($p < 0.001$). This means that the greater the CMT before the operation, the greater the change (reduction) after the operation. We confirmed the same conclusions also for macular volume (table 10).

We attained similar results in the PPV + TRIAM group. We confirmed a statistically significant level in measurements of CMT and macular volume (in both measurements $p < 0.001$). In this group the results of both CMT and macular volume confirm the significance of the statistical differences on the level $p = 0.05$ (table 11).

Complications

The most frequent complications during surgery were retinal ruptures. In the PPV group we treated a rupture in one eye (2.86%) with lasercoagulations and in 6 eyes (17.14%) we used cryocoagulation. In the PPV + TRIAM group we treated ruptures appearing during surgery in 3 eyes (9.09%) with the help of cryocoagulation. Expan-

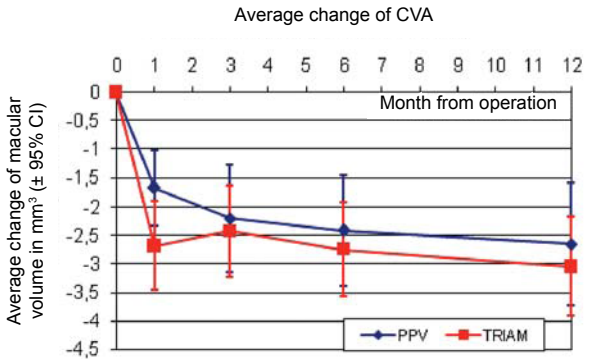
Table 8 Average values of macular volume (mm3)

	Before operation	1st month	3rd month	6th month	12th mont
PPV	11.48	9.82	9.28	9.07	8.83
PPV + TRIAM	10.71	8.03	8.28	7.96	7.66

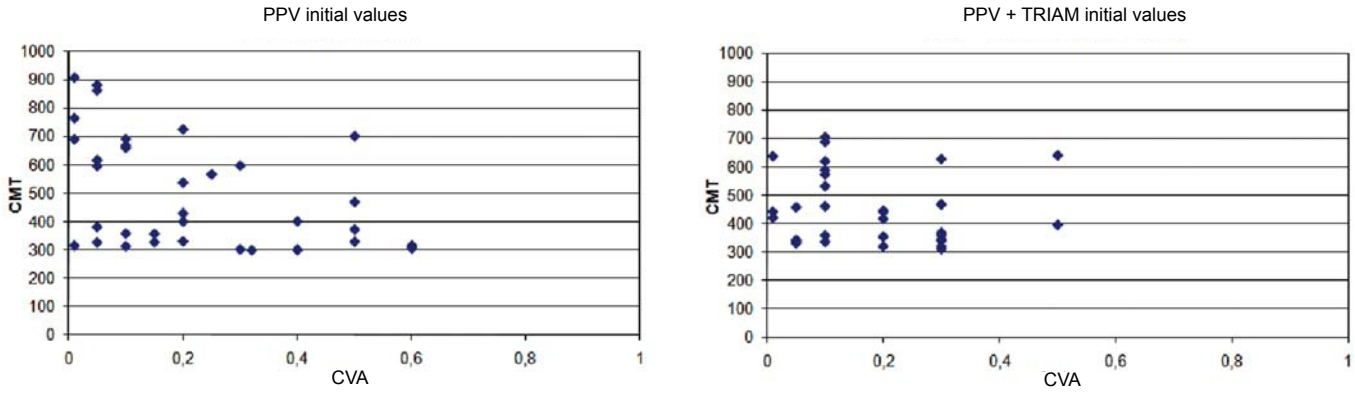
Table 9 Comparison of PPV group with PPV + TRIAM group. Average values of change of macular volume (mm3) before operation up to 12th month

PPV v PPV + TRIAM	Before operation	1st month	3rd month	6th month	12th mont
PPV	0	-1.67	-2.2	-2.42	-2.65
PPV + TRIAM	0	-2.68	-2.43	-2.75	-3.05
	p-value	0.027	0.717	0.759	0.542

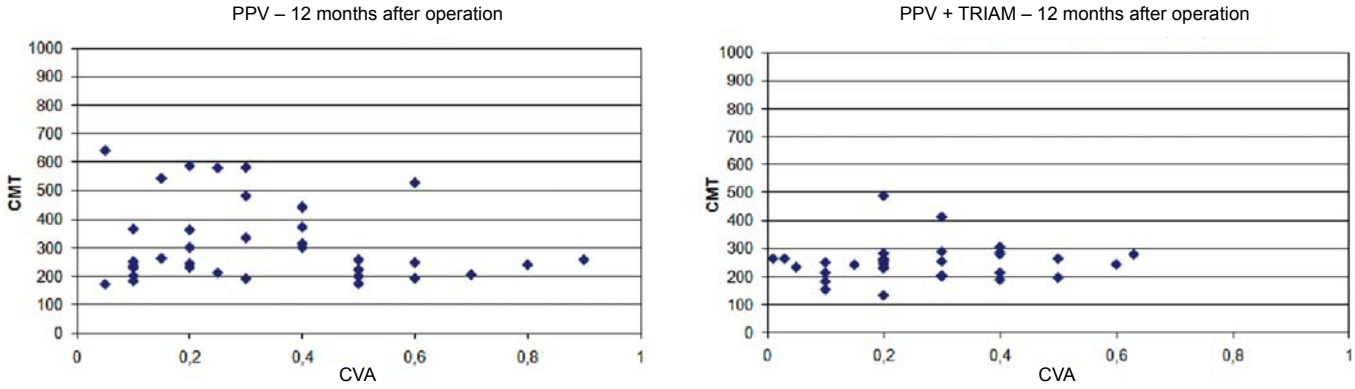
ding SF6 gas was applied to all these eyes at the end of the operation.
In the first year of observation we observed an increase of IOP above 25 mmHg in 5 eyes (14.29%) in the PPV group and in 9 eyes (27.27%) in the PPV + TRIAM group. In all eyes with increased IOP monotherapy was applied. In one eye (2.86%) in the PPV group and three eyes (9.09%) in the PPV + TRIAM group observed before the operation for primary open--angle glaucoma and treated with monotherapy it was necessary to add a further antiglaucoma agent to the



Graph 3 Average change of macular volume (mm³)



Graphs 4, 5 PPV group and PPV + TRIAM group. Initial values – graphic dependency of central visual acuity values on central macular thickness (μm)



Graphs 6, 7 PPV group and PPV + TRIAM group. Graphic dependency of central visual acuity values on central macular thickness (μm) in 12th month

Table 9 Correlation (dependency) between individual parameters before operation and change thereto over the course of 12 months after operation in PPV group

PPV	Correlation coefficient	p-value
Change of CVA vs CVA 0	-0.19	0.28
Change of CMT vs CMT 0	-0.76	<0.001
Change of Volume vs Volume 0	-0.67	<0.001
Change of CVA vs change of CMT	-0.04	0.82
Change of CVA vs change of Volume	0.04	0.84
Change of CMT vs change of Volume	0.76	<0.001
Change of CVA vs CMT 0	-0.115	0.51

Table 10 Correlation (dependency) between individual parameters before operation and change thereto over the course of 12 months after operation in PPV + TRIAM group

PPV + TRIAM	Correlation coefficient	p-value
Change of CVA vs CVA 0	-0.238	0.18
Change of CMT vs CMT 0	-0.916	<0.001
Change of Volume vs Volume 0	-0.948	<0.001
Change of CVA vs change of CMT	-0.094	0.60
Change of CVA vs change of Volume	-0.237	0.18
Change of CMT vs change of Volume	0.823	<0.001
Change of CVA vs CMT 0	0.079	0.66

Table 11 Lens surgery in PPV and PPV + TRIAM groups

Lens operation	Yes	No	Proportion of operated patients
PPV	4	18	18.18%
PPV + TRIAM	11	16	44.0%

treatment. There was a fibrin reaction in PK in 5 eyes (14.29%) in the PPV group and in 4 eyes (12.12%) in the PPV + TRIAM group. In all cases the reaction passed within one week of the operation. Bleeding into the vitreous cavity was found in two eyes (5.71%) in the PPV group and one eye (3.03%) in the PPV + TRIAM group. In all cases it was absorbed spontaneously without the necessity of surgical intervention. Hypotonia on the 1st day after the operation was determined in one eye after 23G PPV. Detachment of the retina and endophthalmitis was not recorded in any eyes.

In both groups we prospectively observed the necessity of lens surgery in the postoperative period and the average time until the lens operation. In the PPV we performed a lens surgery in 4 of 22 phakic eyes (18.18%). At the time of the PPV operation thirteen eyes (37.14%) were pseudophakic. The average time until the lens operation was 8.56 ± 3.11 months. In the PPV + TRIAM group 25 phakic eyes were evaluated. 8 eyes (24.24%) had an artificial intraocular lens before the operation. A lens operation was necessary in 11 eyes (44.0%), the average time until the operation was 6.25 ± 3.65 months. In the PPV + TRIAM group the occurrence of subsequent lens operations was higher than in the PPV group (p = 0.056) (table 12).

DISCUSSION

Diabetic macular edema (DME) represents a serious cause of deterioration of CVA in patients with diabetes. Strict monitoring of the glucose level and blood pressure values, as well as focal/grid lasercoagulation are effective procedures for many patients, but there is also a group of patients in whom a deterioration of CVA occurs (22).

In our observation we evaluated the impact of PPV with MLI peeling on the absorption of DME and resulting CVA. We also observed whether the addition of the application of 4 mg triamcionolone acetonide at the end of the operation and lasercoagulation of the macula 3 weeks after the operation to this operation procedure had a significant impact on the variables we observed. 68 eyes were observed in 59 patients, who were divided into 2 groups: the PPV group included 35 eyes, on which we performed PPV with MLI peeling, the PPV + TRIAM group included 33 eyes, on which we performed PPV with MLI peeling, application of TRIAM and lasercoagulation of the macula 3 weeks after the operation.

One of the most important roles upon the occurrence and persistence of diffuse DME is played by the vitreous area (25, 26). The evidence concerning the role of the vitreous area upon the occurrence and persistence of DME is based on numerous studies. Since 1992, when Lewis et al (20) described the benefit of PPV in 10 eyes with thickened and distended posterior vitreous membrane (PVM) before the macula upon DME, there has been increased interest in vitreoretinal surgery and surgical treatment of DME. In their observation, PPV in connection with the removal of PVM led to absorption of the edema in 10 eyes, with an improvement of CVA in 8 out of 10 eyes. Subsequently further authors have confirmed the positive effect of PPV in the treatment of DME with thickened and distended PVM (12, 14, 24). In the following period a number of retrospective clinical studies were published, which demonstrated that PPV with the remo-

val of PVM upon DME with traction can bring about a reduction of edema and an improvement of visual functions (30, 32). On the other hand, PPV can lead to a reduction of macular edema in eyes with DR, even without the presence of apparent vitreomacular traction (6, 17, 31). La Heij et al. (17) published a study where they described absorption of DME after PPV in 19 eyes without the presence of vitreomacular traction before the operation. Tachi and Ogino (31) observed the effect of PPV in the case of diffuse DME in 58 eyes with attached PVM. After 12 months of observation there was an absorption of the edema in 92% of eyes and improvement of CVA in 53% of eyes. Absorption of edema in patients with diffuse DME is not conditional only upon the relaxation of all tractional forces from the surface of the retina, but probably also upon the elimination of factors increasing permeability, such as VEGF, and probably also better transport and penetration of oxygen and nutrient substances via the vitreous cavity to the macula. During PPV we replace viscous gel with a less viscous infusion solution, which results in increased transport of molecules in the vitreous cavity. On the basis of these changes for example, oxygen may be transported from the well-supplied areas of the retina to the hypoxic areas (28, 29). Holekamp et al. (11), Maeda and Tano (21) and Steffanson et al. (29) demonstrated that PPV reduces hypoxia of the retina in both experimental animals and humans. Some have demonstrated that oxygen treatment reduces the extent of DME and the action of oxygen leads to a reduction of VEGF (23). Consumption of oxygen by the retina is also reduced upon lasercoagulation, which explains its effect in the treatment of DR (29). Antonetti et al. (1) demonstrated that an increase in the VEGF level in the vitreous area is connected with an increase in the level of occlusion and damage to fixed endothelial connections. These changes also contribute to an increase in vascular permeability in patients with DME. It is assumed that the effect of PPV upon absorption of DME is brought about by a combination of both mechanisms by a) relaxation of all tractional forces from the surface of the retina and b) improvement of the supply of oxygen to the retina and reduction of the concentration of factors increasing vascular permeability (11).

Stolba et al. (30) demonstrated in a prospective randomised trial that PPV with MLI peeling is connected with superior functional and anatomical results than the natural course of the disorder. Yanyali et al. (33) observed a superior effect of PPV with MLI peeling on the absorption of DME and CVA in comparison with a single session of grid lasercoagulation. Gandorfer et al. (9), in their small study on 12 patients after PPV with MLI peeling, attained an improvement of CVA by 2 or more rows of Snellen's optotypes in 92% of patients 4-12 weeks after the operation. The occurrence of a new edema or worsening of an existing edema was not observed in a single patient during an average observation period of 16 months (8-31 months). They determined PVM thickened and attached to the macula in 10 patients during the operation. In two patients after PPV they observed a pathological reflex on the surface of the retina, but no membrane before the macula. Pars plana vitrectomy with MLI peeling led to an improvement of CVA and absorption of the edema without the occurrence of new epiretinal membranes in the postoperative period. As a result, complete relaxation of tangential traction and inhibition of reproliferation of fibrous astrocytes is a well considered choice in the treatment of patients with DME and advanced disorder of the vitreomacular interface (9). The mechanism which leads to the absorption of the edema following MLI peeling is probably caused by a complete relaxation of tractional forces, an increase in exchange of substances between the retina and vitreous area (thickened MLI acts as a barrier to diffusion), and thus better oxygenation of the macula (6, 7).

We determined absorption of the edema one year after the operation, CMT < 250 μm, in 45.7% of eyes in the PPV group and in 48.55% of eyes in the PPV + TRIAM group. We achieved a central macular thickness of less than 300 μm in 65.71% of eyes in the PPV group and in 90.9% of eyes in the PPV + TRIAM group, which is a statistically significant difference ($p < 0.001$). We explain the larger number of eyes with CMT < 300 μm as well as the doubling of the reduction of CMT and macular volume in the first month after the operation in the PPV + TRIAM group by means of the application of TRIAM at the end of the operation and lasercoagulation of the macula 3 weeks after the operation. From a number of studies we know that TRIAM is effective in the treatment of DME, improves CVA, reduces CMT and macular volume, but that its effect lasts for only 3 to 6 months after administration in a dose of 4 mg (5, 15). Additional therapeutic procedures, such as lasercoagulation, may further enhance this effect (16). The most marked reduction in macular thickness in eyes following application of TRIAM is achieved in eyes with a vitreous area in the 4th week after administration (4). The average half-life of absorption of 4 mg of TRIAM from an eye with a vitreous area is 18.6 days, and in an eye after PPV 3.2 days (3). Since this period is shorter after vitrectomy, we decided in favour of lasercoagulation of the macula 3 weeks after the operation in all eyes in the given group of patients. By this method we attempted to be as delicate as possible with regard to eye tissues, in particular to the retina during lasercoagulation, and to minimise the risk of development of an edema after lasercoagulation. We believe that after 3 weeks following the operation the anterior segment is stabilised and the patient co-operates better during the procedure.

As in other publications (11, 18, 27), we also did not determine a correlation between change of CVA and reduction in macular thickness, in the 12th month after the operation in the PPV group $r = -0.04$, $p = 0.82$ and in the PPV + TRIAM group $r = -0.094$, $p = 0.60$. We confirmed a correlation only between change of CMT and change in macular volume in the 12th month, in the PPV group $r = 0.76$, $p < 0.001$ and in the PPV + TRIAM group $r = 0.823$, $p < 0.001$. Shah et al. (27) recommend the exercise of caution in any evaluation of the relationship between resulting CVA and the reduction of CMT. Similarly to us, they did not succeed in demonstrating a significant relationship between the values of initial CVA and a reduction in CMT after the operation ($p = 0.63$). They envisage that the cause may be a dysfunction of the photoreceptors upon a chronic edema, damage to the retina caused by repeated lasercoagulations or disorders of macular perfusion. Stolba et al. (30) observed stabilisation of CVA from the 6th month after the operation. We observed a statistically significant change of CVA from the 3rd month after the operation in both groups and we also achieved stabilisation after the 6th month. Pendergast et al. (24) achieved the same results as us in eyes after PPV with distended and thickened RVM on OCT. They achieved stabilisation of ± 1 row in 91% of eyes and deterioration of CVA by 2 or more rows in 9 eyes. In 45 eyes (81.8%) they observed a complete absorption of the edema on average 4.5 months after the operation. According to expectation, the results were worse in eyes with ischemic maculopathy. Kang et al. (16) observed eyes after combined treatment of PPV + TRIAM and lasercoagulation of the macula 2 weeks after the operation. In

all eyes CVA statistically improved in the 3rd month and remained improved also in the 6th and 12th month. They also determined a significant improvement of CVA between the 6th and 12th month. We observed the most marked improvement of CVA in the 3rd and 6th month after the operation (in the PPV group the change of CVA was 0.06 and 0.10; in the PPV + TRIAM group 0.04 and 0.08).

Dillinger and Mester (6) observed 60 eyes after PPV with MLI peeling and referred to an improvement of CVA by 2 or more rows in 46% of cases and a decrease by 2 or more rows in 7%. However, the average observation period was only 3 months. In the PPV group we attained an improvement of CVA in the 12th month of 2 or more rows of Snellen's optotypes in 28.57% of eyes and a stabilisation of ± 1 row in 65.71%, thus stabilisation and improvement combined in 94.29%. In the PPV + TRIAM group we attained an improvement of CVA in the 12th month of 2 or more rows in 21.21% of eyes and stabilisation in 75.76%. We thus attained combined stabilisation and improvement of CVA in 96.27% of eyes. In the 12th month after the operation we did not record any statistically significant difference in CVA between the two groups (p = 0.375). Lee et al. (19) also observed 2 groups of patients on whom PPV or PPV + TRIAM was performed for various vascular retinal disorders. In the early postoperative period (observation period of 2 months) they observed a statistically significant improvement of CVA in both groups, in which the difference between the two groups was not statistically significant (p = 0.19), similarly as in our groups. They indicated triamcinolone acetonide at the end of the operation upon a finding of a clinically significant macular edema, fibrovascular tissues and in patients younger than 40 years of age.

In our group we recorded a statistically significant reduction of both CMT and macular volume from the 1st month after the operation, which lasted until the last check-up. A similar positive impact of PPV with MLI peeling was observed also in other studies (9, 33). Avci et al. (2) observed an absorption or reduction of edema in 81% of eyes with DME and in 92% of eyes with an edema of another etiology. After combination therapy (PPV + TRIAM and lasercoagulation of macula) Kang et al. (16) determined CMT ≤ 250 μm in 67% of eyes over the course of a six-month observation period. Tachi and Ogino (31) observed an absorption of the edema in the first 3 months after the operation in 46.1% of eyes, between the 3rd and 6th month in 20.7% of eyes and between the 6th and 12th month in 31% of eyes. These results demonstrate that even six months after the operation there is still a chance of absorption of the edema.

We did not observe any serious eye complications such as endophthalmitis or retinal detachment. The most frequent complications in the postoperative period were increase in IOP and the necessity of a lens operation. These are the most frequent side effects after application of corticosteroids into the vitreous cavity. In a retrospective study Beer and Bakri (3) observed 43 eyes and determined an increase in IOP of 24 mmHg and more in 48.8% of eyes, and 27.5% of eyes had increased IOP by more than 10 mmHg. Jonas et al. (15) in a study of 75 eyes in 71 patients also recorded an increase in IOP of above 21 mmHg in 52% of eyes after application of TRIAM. This study however has a smaller impact on practice, since they used a dose of 25 mg, which is used far less frequently than the regular dose of 4 mg. We determined an increase of IOP of 25mmHg or more in 14.29% of eyes in the PPV group and in 27.27% of eyes in the PPV + TRIAM group. A limitation of this observation is the fact that the IOP value was determited on the basis of a single measurement before the operation. Furthermore, in patients with glaucoma disorder, each increase in IOP is serious and an increase of IOP to 25mmHg or more may result in serious complications in these patients.

Kang et al. (16) observed an occurrence of retinal swelling in 8 out of 12 eyes (66.7%), and a lens operation was performed on 7 of these eyes. We focused only on the occurrence of lens operations. We did not perform a lens operation together with an operation on the posterior segment in any of the eyes, in order to avoid any potential negative influence on the results of the lens operation. However, during the observation period a lens operation was required on 4 eyes (18.18%) in the PPV group and on 11 eyes (18.18%) in the PPV + TRIAM group. We determined a more frequent occurrence of lens operations in the postoperative period in the PPV + TRIAM group, p = 0.056, which is on the border of statistical significance. The majority of operations were performed between the 6th and the 12th month of the observation period.

CONCLUSION

The results of our observation demonstrate that both of the operation procedures we observed, namely pars plana vitrectomy with peeling of the MLI and pars plana vitrectomy with peeling of the MLI combined with application of 4mg of triamcinolone acetonide at the end of the operation and lasercoagulation of the macula 3 weeks after the operation are effective in the treatment of DME. We did not determine a statistically significant difference between the individual groups in the 12th month after the operation in central visual acuity, central macular thickness and macular volume. The pars plana vitrectomy with peeling of MLI combined with application of 4mg of triamcinolone acetonide at the end of the operation and lasercoagulation of the macula 3 weeks after the operation is connected to a higher occurrence of postoperative complications (increased IOP and lens surgery).

LITERATURE

1. Antonetti, DA., Barbera, AJ., Hollinger, LA. et al.: Vascular endothelial growth factor induces rapid phosphorylation of tight junction proteins occludin and zonula occluden 1. A potential mechanismus for vascular permeability in diabetic retinopathy and tumors. J Biol Chem., 274, 1999; 33: 23463–7.
2. Avci, R., Kaderli, B., Avci, B., et al: Pars plana vitrectomy and removal of the internal limitng membrane in the treatment of chronic macular edema. Graefes Arch Clin Exp Ophthalmol, 242; 2004: 845–852.
3. Beer, PM., Bakri, SJ., Singh, RJ. et al.: Intraocular concentrations and pharmacocinetics of triamcinolone acetonide after a single intravitreal injections. Ophthalmology, 110; 2003: 681–686.
4. Bonini–Filho, MA., Jorge, R., Barbosa, JC. et al.: Intravitreal injection versus sub–Tenons infusion of triamcinolone acetonide for refractory diabetic macular edema: a randomized clinical trial. Invest Ophthalmol Vis Sci, 46; 2005: 3845–3849.
5. Chieh, JJ., Roth, DB., Liu, M. et al.: Intravitreal triamcinolone acetonide for diabetic macular edema. Retina 25; 2005: 828–834.
6. Dillinger, P., Mester, U.: Vitrectomy with removal of the internal limiting membrane in chronic diabetic macular oedema. Graefes Arch Clin Exp Ophthalmol, 242, 2004, 630–637.

7. Ducournau, D., Ducournau, Y.: A closer look at the ILM. Retinal Physician supplementum, July/August, 2008: 4–15.
8. Early Treatment of Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Graefes Arch Clin Exp Ophthalmol, 103; 1985: 1796–1806.
9. Gandorfer, A., Messmer, E., Ulbig, MW. et al.: Resolution of diabetic macular edema after surgical removal of the posterior hyaloid and the inner limiting membrane. Retina, 20, 2000, 123–133.
10. Gaucher, D., Tadayoni, R., Erginay, A. et al.: Optical coherence tomography assessment of the vitreoretinal relationship in diabetic macular edema. Am J Ophthalmol, 139; 2005: 807–813.
11. Haller JA., Qin H., Apte RS. et al.: Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. Ophthalmology, 117; 2010: 1087–1093.
12. Harbour, JW., Smiddy, WE., Flynn, Jr. HW. et al.: Vitrectomy for diabetic associated with a thickened and taut posterior hyaloid membrane. Am J Ophthalmol, 121; 1996: 405–413.
13. Holekamp, NM., Shui, YB., Beebe, DC. et al.: Vitrectomy surgery increases oxygen exposure to the lens: a possible mechanism for nuclear cataract formation. Am J Ophthalmol, 139; 2005: 302–310.
14. Jahn, CE., Topfner, L., von Schutz, K.et al.: Improvement of visual acuity in eyes with diabetic macular edema after treatment with pars plana vitrectomy. Ophthalmologica, 218; 2004: 378–384.
15. Jonas, JB.: Intravitreal triamcinolone acetonide for diabetic retinopathy. Dev Ophthalmol. Basel, Karger, 2007; vol. 39: 96–110.
16. Kang SW., Park SC., Kang JH.: Triple therapy of vitrectomy intravitreal triamcinolone and macular laser photocoagulation for intractible diabetic macular edema. Am J Ophthalmol 144; 2007: 878–885.
17. La Heij, EC., Hendrikse, F., Kessels, AG. et al.: Vitrectomy results in diabetic macular edema without evident vitreomacular traction. Graefes Arch Clin Exp Ophthalmol, 239; 2001: 264–270.
18. Larrson, J., Zhu, M., Sutter, F. et al.: Relation between reduction of foveal thickness and visual acuity in diabetic macular edema treated with intravitreal triamcinolone. Am J Ophthalmol, 139; 2005: 802–806.
19. Lee, GW., Ahn, AK., Park, YG.: Intravitreal triamcinolone reduces the morphologic changes of ciliary body after pars plana vitrectomy for retinal vascular diseases. Am J Ophthalmol, 145; 2008: 1037–1044.
20. Lewis, H., Abrams, GW., Blumenkraz, MS. et al.: Vitrectomy for diabetic macular traction and edema associated with posterior hyaloid traction. Ophthalmology, 99; 1992: 753–759.
21. Maeda, N., Tano, Y.: Intraocular oxygen tension in eyes with proliferative diabetic retinopathy with and without vitreous. Graefes. Arch. Clin. Exp. Ophthalmol., 234 (Suppl I); 1996: S66–S69.
22. Mayer, C.: Current treatment approaches in diabetic macular edema. Ophthalmologica, 221; 2007: 118–131.
23. Nguyen, QD., Shah, SM., Van Anden, E. et al.: Supplemental oxygen improves diabetic macular edema: a pilot study. Invest Opthalmol Vis Sci, 45; 2004: 617–624.
24. Pendergast, SD., Hassan, TS., Williams, GA. et al.: Vitrectomy for diffuse diabetic macular edema associated with a taut premacular posterior hyaloid. Am J Opthalmol, 130; 2000: 178–186.
25. Sebag, J., Buckingham, B., Charles, MA. et al.: Biochemical abnormalities of vitreous in humans with proliferative diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol, 110; 1992: 1472–1476.
26. Sebag, J.: Vitreous anatomy and vitreomacular interface. Boston, Butterworth–Heinemann, 1998: s. 1–23.
27. Shah, SP., Patel, M., Thomas, D., et al.: Factors predicting outcome of vitrectomy for diabetic maculatr edema: results of prospective study. Br J Ophthalmol, 90; 2006: 33–36.
28. Steffanson, E.: Physiology of vitreous surgery. Graefes Arch Clin. Exp. Opthalmol., 247; 2009: 147–163.
29. Steffanson, E.: The therapeutic effects of retinal laser treatment and vitrectomy: a theory based on oxygen and vascular physiology. Acta Ophthalmol Scand, 79; 2001: 435–440.
30. Stolba, U., Binder, S., Gruber, D. et al.: Vitrectomy for persistent diffuse diabetic macular edema. Am J Ophthalmol, 140; 2005: 295–301.
31. Tachi, N., Ogino, N.: Vitrectomy for diffuse macular edema in cases of diabetic retinopathy. Am J Ophthalmol, 122; 1996: 258–260.
32. Yamamoto, T., Akabane, N., Takeuchi, S.: Vitrectomy for diabetic macular edema: The role of posterior vitreous detachment and epimacular membrane. Am J Ophthalmol, 132; 2001: 369–377.
33. Yanyali, A., Nohatcu, AG., Horozoglu, F. et al.: Modified grid laser photocoagulation versus pars plana vitrectomy with internal limiting membrane removal in diabetic macular edema. Am J Ophthalmol, 139; 2005: 795–801.