https://doi.org/10.17816/mechnikov47394

COMPARATIVE ANALYSIS OF THE EFFECTIVENESS OF ANTIANGIOGENIC THERAPY AND VITRECTOMY IN THE TREATMENT OF DIABETIC MACULAR EDEMA OCCURRING AGAINST THE BACKGROUND OF THE VITREORETINAL INTERFACE PATHOLOGY

E.V. Boiko[1–3], D.H. Oskanov[1], S.V. Sosnovskii[1]

[1] Interindustry Research and Technology Complex "Eye microsurgery" n.a academician S.N. Fyodorov", Saint Petersburg, Russia;
[2] North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia;
[3] Military Medical Academy named after S.M. Kirov, Saint Petersburg, Russia

For citation: Boiko EV, Oskanov DH, Sosnovskii SV. Comparative analysis of the effectiveness of antiangiogenic therapy and vitrectomy in the treatment of diabetic macular edema occurring against the background of the vitreoretinal interface pathology. *Herald of North-Western State Medical University named after I.I. Mechnikov*. 2020;12(4):55-60. https://doi.org/10.17816/mechnikov47394

Received: October 20, 2020 Revised: November 12, 2020 Accepted: December 14, 2020

Background. Diabetic macular edema is a specific complication of diabetes. Antiangiogenic therapy is an effective treatment for diabetic macular edema. Another manifestation of diabetic retinal damage is a change in the vitreoretinal interface. There is evidence of the effectiveness of vitrectomy in the treatment of other ophthalmic diseases with pathology of vitreoretinal interface.

Purpose. Comparative analysis of the effectiveness of antiangiogenic therapy and vitrectomy in the treatment of diabetic macular edema occurring against the background of the vitreoretinal interface pathology.

Materials and methods. The study involved 60 patients (60 eyes) with diabetic macular edema accompanied by vitreoretinal interface pathology. The patients were divided into 2 groups: group 1 — 30 eyes, which received antiangiogenic therapy with intravitreal injections of ranibizumab; group 2 — 30 eyes, on which vitrectomy was performed with removal of the internal limiting membrane. The observation period was 12 months.

Results. In group 1, a significant increase in visual acuity was obtained 1 month after the intravitreal injections. During the observation and performing, if necessary, intravitreal injections, visual acuity decreased and by 12 months did not statistically differ from the initial one. In group 2, there was a gradual reliable increase in the visual acuity.

A decrease in retinal thickness in the second group was significantly greater by the end of the study.

The average number of intravitreal injections required during the observation in the first group was significantly greater than in the second group.

Conclusions. In the patients with diabetic macular edema against the background of pathology of the vitreoretinal interface, vitrectomy led to a significant increase in visual acuity by 12 months of observation, in contrast to the patients receiving antiangiogenic therapy only. In the patients with diabetic macular edema and pathology of the vitreoretinal interface, complex treatment (antiangiogenic therapy + vitrectomy) led to a significant decrease in the thickness of the retina and the number of injections of angiogenesis inhibitors.

Keywords: diabetic macular edema; vitreoretinal interface; antiangiogenic therapy; vitrectomy.

СРАВНИТЕЛЬНЫЙ АНАЛИЗ ЭФФЕКТИВНОСТИ АНТИАНГИОГЕННОЙ ТЕРАПИИ И ВИТРЭКТОМИИ В ЛЕЧЕНИИ ДИАБЕТИЧЕСКОГО МАКУЛЯРНОГО ОТЕКА НА ФОНЕ ПАТОЛОГИИ ВИТРЕОРЕТИНАЛЬНОГО ИНТЕРФЕЙСА

Э.В. Бойко[1–3], Д.Х. Осканов[1], С.В. Сосновский[1]

[1] Федеральное государственное автономное учреждение «Национальный медицинский исследовательский центр «Межотраслевой научно-технический комплекс „Микрохирургия глаза“ им. академика С.Н. Федорова» Министерства здравоохранения Российской Федерации, Санкт-Петербургский филиал;
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Северо-Западный государственный медицинский университет им. И.И. Мечникова» Министерства здравоохранения Российской Федерации;
[3] Федеральное государственное бюджетное военное образовательное учреждение высшего образования «Военно-медицинская академия им. С.М. Кирова» Министерства обороны Российской Федерации

Для цитирования: Бойко Э.В., Осканов Д.Х., Сосновский С.В. Сравнительный анализ эффективности антиангиогенной терапии и витрэктомии в лечении диабетического макулярного отека на фоне патологии витреоретинального интерфейса // Вестник Северо-Западного государственного медицинского университета им. И.И. Мечникова. – 2020. – Т. 12. – № 4. – С. 55–60. https://doi.org/10.17816/mechnikov47394

Поступила: 20.10.2020 Одобрена: 12.11.2020 Принята: 14.12.2020

◆ ***Актуальность.*** Диабетический макулярный отек — специфическое осложнение сахарного диабета, снижающее качество жизни больного. Эффективным методом лечения диабетического макулярного отека является антиангиогенная терапия. Другое проявление диабетического поражения сетчатки — изменение витреоретинального интерфейса. В отдельных исследованиях показано влияние патологии витреоретинального интерфейса на эффективность антиангиогенной терапии диабетического макулярного отека. Представлены данные об эффективности витрэктомии в лечении других офтальмологических заболеваний с патологией витреоретинального интерфейса.

Цель — сравнительный анализ эффективности антиангиогенной терапии и витрэктомии в лечении диабетического макулярного отека на фоне патологии витреоретинального интерфейса.

Материалы и методы. Исследовано 60 пациентов (60 глаз) с диабетическим макулярным отеком, сопровождающимся патологией витреоретинального интерфейса по данным оптической когерентной томографии. Пациенты разделены на две группы: в первой группе (30 глаз) проводили антиангиогенную терапию в виде интравитреального введения ранибизумаба; во второй группе (30 глаз) выполняли витрэктомию с удалением внутренней пограничной мембраны. Срок наблюдения составил 12 мес.

Результаты. В первой группе через 1 мес. после интравитреального введения получено достоверное увеличение остроты зрения. В ходе наблюдения и выполнения при необходимости интравитреального введения острота зрения уменьшалась и к 12-му месяцу статистически не отличалась от исходной. Во второй группе через 1 и 3 мес. после витрэктомии не отмечено значимого изменения остроты зрения. Однако затем наблюдалось постепенное достоверное ее увеличение.

В обеих группах зафиксировано достоверное уменьшение толщины сетчатки в период наблюдения. С 3-го месяца снижение толщины сетчатки во второй группе было значимо больше по сравнению с первой группой. К концу исследования толщина сетчатки во второй группе близка к нормальной в отличие от первой группы.

Среднее количество интравитреальных введений, понадобившихся в ходе наблюдения в первой группе, было значимо больше, чем во второй.

Выводы. У пациентов с диабетическим макулярным отеком на фоне патологии витреоретинального интерфейса выполнение витрэктомии приводит к значимому повышению остроты зрения к 12-му месяцу наблюдения в отличие от пациентов, получающих только антиангиогенную терапию. У пациентов с диабетическим макулярным отеком и патологией витреоретинального интерфейса комплексное лечение (антиангиогенная терапия + витрэктомия) позволяет достоверно значимо уменьшить толщину сетчатки и количество инъекций ингибиторов ангиогенеза.

◆ **Ключевые слова:** диабетический макулярный отек; витреоретинальный интерфейс; антиангиогенная терапия; витрэктомия.

Background

Diabetes mellitus (DM) is a disease that often results in visual function disablement among people aged 40–70 years old [1]. Diabetic macular edema (DME) is a serious diabetes complication that affects a patient's quality of life, and the incidence of DME among diabetic patients ranges from 3%–29% [2].

Anti-angiogenic therapy by angiogenesis inhibitor intravitreal administration (AIIVA) is currently considered the "gold standard" of DME treatment. Clinical practice and data from multicenter studies prove the efficiency of this method [3–5].

Meanwhile, another manifestation of diabetic retinal disorder, which is often combined with DME, is a change in the vitreoretinal interface (VRI) [6]. Some studies have revealed the effect of VRI pathology on the efficiency of anti-angiogenic therapy for DME [7]. This determines the expediency of vitrectomy with the removal of the posterior hyaloid and the internal limiting membrane, thereby representing an effective method of treating other ophthalmic

Table 1 / Таблица 1

Characteristics of patients in each study group
Характеристики исследуемых групп

Characteristics	Group 1	Group 2
Number of patients (eyes)	30 (30)	30 (30)
Gender (men/women)	15/15	10/20
Average age, years	71 ± 5.2	69 ± 4.4
Average visual acuity	0.30 ± 0.15	0.23 ± 0.13
Average thickness of the central retina, microns	598.5 ± 111.4	573.3 ± 123.3

diseases with VRI pathology. Considering the data on the influence of pathological changes in VRI on the efficiency of anti-angiogenic therapy for DME, vitrectomy should be considered as an alternative and, possibly, the preferred method of treatment in DME.

This work aimed to perform a comparative analysis of the efficiency of anti-angiogenic therapy and vitrectomy in treatment of DME in case of VRI pathology.

Materials and methods

The study included 60 patients (60 eyes) with DME combined with concomitant VRI pathology, as confirmed by the data of optical coherence tomography. All patients were diagnosed with type 2 DM and compensated glycemic level (glycated hemoglobin lower than 7.5%). An optical coherence tomogram revealed one of the variants of VRI pathology (epiretinal fibrosis, vitreomacular adhesion, vitreomacular traction, and extramacular epiretinal membrane). Except for DME, any other ophthalmic pathology capable of reducing visual acuity (tractional retinal detachment, macular hole, occlusion of retinal veins or arteries, glaucoma, etc.) was used as a criterion for exclusion from the study.

The DME patients were distributed into two groups. Group 1 consisted of patients who received three AIIVAs at the start of DME therapy and continued anti-angiogenic therapy as the circumstances required. Anti-angiogenic therapy with ranibizumab administered at a dose of 0.5 mg was performed according to the standard protocol. Group 2 included patients who received three AIIVAs at the start of DME therapy and subsequently underwent surgical treatment in the scope of vitrectomy with peeling of the internal limiting membrane. Surgical techniques included subtotal three-port 25 G vitrectomy, aspiration induction of posterior hyaloid detachment followed by its elevation and removal, and staining of the internal limiting membrane and its removal with forceps. In the presence of indications due to the recurrence of macular edema, AIIVA was performed on the patients in the postoperative period.

Patients in both groups were randomized based on the baseline generally accepted indicators analyzed in the medical literature on anti-angiogenic therapy for DME, namely, visual acuity and central retinal thickness.

The follow-up period was 12 months.

Table 1 presents the main characteristics of patients in the study groups.

Each patient underwent a monthly standard ophthalmologic examination, which included visometry according to the Snellen eye chart and spectral optical coherence tomography. The criteria for evaluating efficiency were visual acuity and thickness of the central retina at the end of the study as well as the frequency of AIIVA per year.

Results

In accordance with the aim of this study, we analyzed the changes in visual acuity in patients of the studied groups (Table 2).

In Group 1, the visual acuity increased statistically significantly from 0.30 ± 0.15 to 0.39 ± 0.2 one month after undergoing AIIVA. In the course of further follow-up and, if necessary, another round of AIIVA, visual acuity decreased

Table 2 / Таблица 2

Dynamics of visual acuity in patients with diabetic macular edema under different treatment options
Динамика остроты зрения у пациентов с диабетическим макулярным отеком при различных вариантах лечения

Group	Visual acuity according to the Snellen eye chart					
	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12
One	0.30 ± 0.15	0.39 ± 0.2[1]	0.34 ± 0.18	0.34 ± 0.16	0.31 ± 0.17	0.33 ± 0.19
Two	0.23 ± 0.13	0.22 ± 0.14[3]	0.28 ± 0.15	0.32 ± 0.18[1]	0.34 ± 0.2[1]	0.37 ± 0.21[2]

[1] $p < 0.05$ compared to the baseline; [2] $p < 0.001$ compared to the baseline; [3] $p < 0.001$ compared to Group 1.

Table 3 / Таблица 3

Dynamics of central retinal thickness in patients with diabetic macular edema under different treatment options
Динамика толщины центральной сетчатки у пациентов с диабетическим макулярным отеком при различных вариантах лечения

Group	Central retinal thickness, microns					
	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12
One	598.5 ± 111.4	486.1 ± 83.2[1]	509.3 ± 90[1]	506.8 ± 93.2[1]	488.9 ± 99.6[1]	516.8 ± 130.1[1]
Two	573.3 ± 123.3	442.5 ± 112.6[1]	400.3 ± 66.3[1,2]	405.9 ± 86.9[1, 2]	390.9 ± 85.7[1, 2]	383.6 ± 64.9[1, 2]

[1] $p < 0.001$ compared to the baseline; [2] $p < 0.001$ compared to the group 1.

to 0.33 ± 0.19, which did not differ statistically from the initial visual acuity.

In Group 2, no statistically significant change in visual acuity was revealed 1 and 3 months after vitrectomy. However, eventually, there was a gradual statistically significant increase in visual acuity from 0.32 ± 0.18 at month 6 to 0.37 ± 0.21 at month 12.

Table 3 presents the results of the analysis of changes in the central retina thickness in the groups during the follow-up period.

Analysis of the results presented in Table 3 indicated a statistically significant decrease in the retinal thickness in both groups during the entire follow-up period. However, starting from month 3, the decrease in the central retinal thickness in Group 2 was significantly greater than that in Group 1. By the end of the study, the retinal thickness in Group 2 was close to normal (383.6 ± 64.9), while it was statistically significantly greater in Group 1 (516.8 ± 130.1, $p < 0.001$).

Furthermore, the analysis of the number of injections performed showed that during the follow-up period, the frequency of AIIVA per year in Group 1 was 5.7 ± 0.9, which was significantly higher than in Group 2 (0.7 ± 1.2, $p < 0.001$).

Discussion

Pathological changes in VRI are not always an indication for vitrectomy. Such cases include the following:

— vitreomacular traction with an extrafoveolar location, which does not cause traction deformity of the macula;
— extrafoveolar vitreomacular adhesion, which is not considered by some authors as a pathology;
— epiretinal fibrosis, whose surface is not grossly deformed, in the presence of retinal edema; and
— extramacular epiretinal membrane, which forms tangential traction reaching the macular region.

Under the classification of The International Vitreomacular Traction Study Group [8], these changes are not considered as a separate pathology of VRI. In DME patients, these were revealed both during initial diagnostics and during regular anti-angiogenic therapy. However, they are usually not considered as invariable indications for vitrectomy. In accordance with the existing contemporary approach to the treatment of DME,

such patients typically receive anti-angiogenic therapy. However, the absence of a persistent effect from the regular administration of angiogenesis inhibitors in the future suggests that there are signs of DME refractoriness in the therapy performed. The therapeutic approach can consist either in the continuation of anti-angiogenic therapy, which provides a short-term effect, or changing to other algorithms focused on alternative pathogenetic links of the disease. In our case, vitrectomy was chosen as an algorithm as part of a method of influencing the VRI pathology.

The current study's findings revealed that the continuation of regular anti-angiogenic therapy for DME with concomitant pathology of VRI led to a short-term increase in visual acuity in month 1 after the onset of treatment. In the future, the achieved functional effect may decrease to the initial indices of visual acuity. The continuation of regular anti-angiogenic therapy with a follow-up period of up to 12 months promoted the stabilization of functional indicators. At the same time, in the group of patients who underwent vitrectomy, a progressive increase in visual acuity was registered compared to the initial values by the end of the follow-up period.

Optical coherence tomography data demonstrate clearly that, in DME with concomitant VRI pathology, the retinal thickness decreased progressively in the central zone both in the anti-angiogenic therapy group and in the vitrectomy group. This thickness was significantly less than the initial values by the end of the follow-up period. At the same time, by the end of the follow-up period, the average retinal thickness in the vitrectomy group had decreased to almost normal values, while in the anti-angiogenic therapy group, residual retinal edema was registered. Furthermore, the decrease in retinal thickness in the vitrectomy group was significantly greater than in the anti-angiogenic therapy group as early as 3 months after the case follow-up.

Moreover, a significantly greater number of intravitreal injections of an angiogenesis inhibitor were required to relieve the retinal edema in the anti-angiogenic therapy group during the entire follow-up period compared with the vitrectomy group.

The obvious efficiency of vitrectomy illustrates the importance of such a link in the DME pathogenesis as a traction component. In this regard, it can be assumed that DME is also induced by the traction component in patients with a vitreoretinal interface pathology in DM. Therefore, in the absence of efficiency of the anti-angiogenic therapy, the change to vitrectomy should be considered.

Conclusions

1. In DME patients with concomitant pathology of VRI, vitrectomy significantly improved visual acuity by the end of month 12 of the case follow-up, in contrast to patients receiving only regular anti-angiogenic therapy.
2. In DME patients with VRI pathology, comprehensive treatment (anti-angiogenic therapy + vitrectomy) resulted in a significant decrease in central retinal thickness and the number of injections of angiogenesis inhibitors.

References

1. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-Week Results From the VISTA and VIVID Studies. *Ophthalmology*. 2015;122(10):2044–2052. https://doi.org/10.1016/j.ophtha.2015.06.017.
2. Musat O, Cernat C, Labib M, et al. Diabetic macular edema. *Rom J Ophthalmol*. 2015;59(3):133–136.
3. Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): A 12-month, randomized, controlled, double-masked, multicenter phase II study. *Diabetes Care*. 2010;33(11):2399–2405. https://doi.org/10.2337/dc10-0493.
4. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011;118(4):615–625. https://doi.org/10.1016/j.ophtha.2011.01.031.
5. Нероев В.В. Современные аспекты лечения диабетического макулярного отека // Российский офтальмологический журнал. – 2012. – Т. 5. – № 1. – С. 4–7. [Neroev VV. Current issues in the treatment of diabetic macular edema. *Russian Ophthalmological Journal*. 2012;5(1):4–7. (In Russ.)]
6. Wong Y, Steel DH, Habib MS, et al. Vitreoretinal interface abnormalities in patients treated with ranibizumab for diabetic macular oedema. *Graefes Arch Clin Exp Ophthalmol*. 2017;255(4):733–742. https://doi.org/10.1007/s00417-016-3562-0.

7. Kulikov AN, Sosnovskii SV, Berezin RD, et al. Vitreoretinal interface abnormalities in diabetic macular edema and effectiveness of anti-VEGF therapy: an optical coherence tomography study. *Clin Ophthalmol*. 2017;11:1995–2002. https://doi.org/10.2147/OPTH.S146019.

8. Duker JS, Kaiser PK, Binder S, et al. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. *Ophthalmology*. 2013;120(12):2611–2619. https://doi.org/10.1016/j.ophtha.2013.07.042.

◆ **Information about the author** *(Адрес автора для переписки)*

Dzhambulat H. Oskanov / Джамбулат Хусенович Осканов
https://orcid.org/0000-0001-8842-2643
E-mail: oskanovd@mail.ru