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Original Article / Оригинални рад

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The influence of intravitreally applied triamcinolone acetonide on vitreal hemorrhage resorption and visual acuity in patients with proliferative diabetic retinopathy

Утицај интравитреално апликованог триамцинолон-ацетонида на ресорпцију витреалне хеморагије и видну оштрину код болесника са пролиферативном дијабетесном ретинопатијом

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SUMMARY

Introduction/Objective Vitreal hemorrhage (VH) is one of the possible complications of the diabetic retinopathy which is followed by intensive decrease of visual acuity. Corticosteroides are commonly used in treatment of different retinal diseases, due to their anti-inflammatory and anti-angiogenetic effect. Triamcinolone acetonide applied invtravitreally remains in the eye for several months, releases its crystals and decreases the density of vitreal hemorrhage.

The aim of this study was to evaluate the efficacy of 20 mg intravitreal triamcinolone acetonide for the managementof long lasting VH, occurred as a complication of proliferative diabetic retinopathy (PDR) in non-vitrectomized eyes.

Methods In prospective study, from January 1st 2015 until the January 1st 2016, 24 patients with VH who received intravitreal triamcinolone acetonide, were compared to 21 patients from the control group (patients with PDR and similar degree of VH). All patients passed ophthalmological examination at the beginning of the study, 7 days, 1, 3, 6, 9 and 12 months after intravitreal application of 20mg triamcinolone acetonide. Besides VH and visual acuity, intraocular pressure and cataract development were also analyzed.

Results Statistically significant difference was recorded 1st and 3rd month after the usage of triamacinolone, in the density of vitreal hemorrhage and visual acuity. Twenty-nine percent of patients had temporally intraocular pressure rise after the intravitreal triamacinolone application, and 4.1% of patients ended the study with the developed cataract.

ConclusionIntravitreally applied triamcinolone acetonide has moderate and temporary influence on the velocity of vitreal hemorrhage reabsorption. It can be useful treatment option when the vitrectomy in not possible.

Key words: triamcinolone acetonide, vitreal hemorrhage, intravitreal injection, intraocular pressure

САЖЕТАК

Увод/Циљ Витреална хеморагија (ВХ) једна је од могућих компликација дијабетесне ретинопатије, праћена интензивним падом видне оштрине. Кортикостероиди се учестало користе у лечењу различитих ретиналних обољења, захваљујући свом анти-инфламаторном и анти-ангиогенетс-комефекту. Тримацинолон ацетонид апликован интравитреално задржава се у оку неколико месеци, отпушта своје кристале и смањује густину ВХ.

Циљ ове студије је да процени ефикасност 20 милиграма интравитреално апликованог триамцинолон-ацетонида у третману дуготрајне ВХ као компликације пролиферативне дијабетесне ретинопатије (ПДР) код невитректомисаних очију.

Методе У проспективној студији, у 2015. години, упоређени су 24 болесника са ВХ и интравитреално апликованим триамцинолон-ацетонидом са 21 болесником из контролне групе (болесници са ПДР и сличним степеном ВХ). Сви болесници су имали комплетан офталмолошки преглед на почетку студије, 7 дана, 1, 3, 6, 9 и 12 месеци после интравитреалне апликације 20 милиграма триамцинолон-ацетонида. Поред ВХ и видне оштрине, анализирани су и интраокуларни притисак и развој катаракте.

Резултати Статистички значајна разлика забележена је 1. и 3. месеца после употребе триамцинолона у густини ВХ и видној оштрини. Код 29% болесника забележен је привремени скок интраокуларног притиска после интравитреалне примене триамцинолона, а 4,1% пацијента завршило је студију са развијеном катарактом.

Закључак Интравитреално апликован триамцинолон-ацетонид има умерен и привремен ефекат на брзину реапсорпције ВХ. То може представљати корисну терапијску могућност када витректомија није могућа.

Кључне речи триамцинолон ацетонид, витреална хеморагија, интравитреална инјекција, интраокуларни притисак

INTRODUCTION

Vitreal hemorrhage (VH) represents a significant complication of proliferative diabetic retinopathy which causes serious decrease of visual acuity [1]. There are many factors that

distinguish vitreal hemorrhage from other hemorrhages: long-time survival of intact red blood cells, instant clot formation, slow fibrin lysis, inactivated early polymorphonuclear cellular response. It is known that vitreal hemorrhage has clearance of only 1% per day [2]. The accepted method for treatment of vitreous hemorrhage is pars plana vitrectomy [1].

Due to their anti-inflammatory and anti-angiogenetic influences, corticosteroides are commonly used in treatment of different retinal disorders. As it is reported by many studies, triamcinolone acetonide applied intravitreally (IVTA) has shown an effect in treatment of macular edema or proliferative diabetic retinopathy and proliferative vitreoretinopathy [3-5]. Serving as an adjuvant therapy, IVTA acts like a depot, releasing crystals into the vitreal cavity [5]. The usage of triamcinolone acetonide is the reduction of intra and postoperative inflammation, vascular permeability and reproliferation. [6] Triamcinolone acetonide can also be effective for rapid clearing of recurrent postvitrectomy diabetic vitreal hemorrhage [6].

The study was conducted with the aim to evaluate the efficacy of 20 mg IVTA in the adjuvant treating of long lasting VH, in patients with proliferative diabetic retinopathy in non-vitrectomized eyes. We measured the density of vitreal hemorrhage and recorded the influence that IVTA had on the visual acuity, cataract development and intraocular pressure (IOP) rise.

MATERIALS AND METHODS

A prospective, comparative study included two groups of patients. The first group (IVTA group) contained 24 patients with, long lasting vitreal hemorrhage of a various density which occurred as a complication of proliferative diabetic retinopathy. They were recruited for intravitreal application of triamcinolone acetonide. Second group had 21 participants with proliferative diabetic retinopathy and with similar degree of vitreal hemorrhage (control group). Gender and age were matched between groups. Study was performed from January 1st 2015 until January 1st 2016, at the Clinic of Ophthalmology, Clinical Centre Kragujevac, Serbia. With the approval of institutional Ethics Committee and according to the tenets of the Declaration of Helsinki, all enrolled patients gave their written consent at the beginning of the investigation. All the patients from the first group were acquainted that this was an off-label use of triamcinolone acetonide and signed an informed consent.

Patients have passed a complete ophthalmological examination: visual acuity, intraocular pressure measurement, slit lamp, fundus examination and ocular ultrasonography. Those examinations were performed before the IVTA application, at the visits after seven days, one month, three months, six, nine and twelve months.

The degree of intravitreal hemorrhage was scaled according to the diabetic retinopathy vitrectomy study grading system [7] (Table 1). In this study, we examined patients who received IVTA, by comparing the IVTA effect on VH resorption and VA with the control group. IOP rise and cataract development were also follow up parameters, as possible complications after ocular steroid administration [8].

Table 1. Diabetic retinopathy vitrectomy study grading system.

Grade 0	No vitreous hemorrhage
Grade 1	Mild vitreous hemorrhage with visible fundus details
Grade 2	Moderate vitreous hemorrhage with no visible fundus details but with an orange fundus reflex
Grade 3	Severe vitreous hemorrhage with no retinal details and no orange fundus reflex.

Excluded criteria for the patients were: preexisting glaucoma, uveitis, myopia, ocular trauma, earlier intraocular surgery, cataract, and retinal detachment confirmed by ocular ultrasonography or fundoscopic examination. Also, patients with previous exposure to the topical, intraocular or systemic steroids were excluded. If any patients had developed some other complication of the diabetic retinopathy,during the period of the study, such as diabetic macular edema, they would have been excluded too.

The intravitreal injection of 20mg triamcinolone acetonide was given to all patients in the operation theatre under sterile conditions. As we mentioned earlier, patients agreed to receive an off-label triamcinolone acetonide and signed an informed consent. The usage of multiply sedimentation was performed to get a wanted dose of 20mg triamcinolone acetonide. The crystalline cortisone was adopted after aspirating 1 mm bottle which contained about 40 mg TA (®Kenalog, Bristol Myers Squibb, New York) into syringe of 1 mm. After leaving the syringe into vertical position for 20 minutes, the first sedimentation was done. The upper, unsedimented part, was gently ejected trough the syringe. Sedimented part, about 0.2 ml, was then mixed with Ringer's solution until the syringe was fulfilled again. After 5 minutes in vertical position, from the syringe was again eliminated unsedimented part, about 0.8 ml. This procedure was repeated once more. After this triple sedimentation, in the syringe left about 0.2 ml, with about 20 mg triamcinolone acetonide.

Periocular and ocular area were sterilized using 5 and 10% povidone iodine. TA was injected into the central parts of the vitreal cavity. Under the topical anesthesia, using 27 gauge needle, 3.5 mm from the limbus, triamcinolone acetonide was implemented. When the procedure was done, the patients remained in upright position for the next two hours. Topical ciprofloxacin (®Floxal, DR.Gerhard Mann, Chem.-Pharm. Fabrik GmbH, Berlin, Germany) was prescribed five times per day, for the next seven days.

Statistical methods

SPSS ver.22 statistical software package (SPSS Inc., Chicago, IL) was used for all calculations in the study. We used Freidman's test in testing the evolution of vitreal hemorrhage through the period of twelve months. For comparison of the other variables, such as IOP, visual acuity, or cataract development Student t-test was used. Value $p<0.05$ was accepted as statistically significant.

RESULTS

Examined patients from the first group had a mean age of 56.24±5.5 years, while those from the control group were 54.15±4.8. No statistical significance was recorded among patients age ($p = 0.43$). In both groups female to male ratio was approximately equal.

Every patient passed a complete ophthalmological examination in every visit during the followed up period (Figures 1, 2, & 3). According to the density of vitreal hemorrhage, examined patients were divided into four grades and statistically analyzed. Visual acuity was measured for every grade separately. Mean visual acuity in the 0 grade was 0.9±0.1, in the I grade was 0.6±0.17. The second and third grades characterized intensive decrease of visual acuity, 0.3±0.15 and 0.03±0.01.

At the beginning of the research, in IVTA group were 0 patients with the 0 grade, 7 with the I grade, 10 with the II, and 7 patients with the III grade of vitreal hemorrhage. Control group had also 0 patients with the 0 grade, but 6 patients with the I grade, 9 patients with the II grade, and 6 patients with the III grade. No statistical significance was seen (p=0.99) between the groups. At that time none of the patients had IOP over the 21mm Hg or any sings of the cataract development. Mean visual acuity in the first group was 0.30 ± 0.05, while in the second group was 0.31±0.03, without statistically significant difference between the groups (p=0.68).

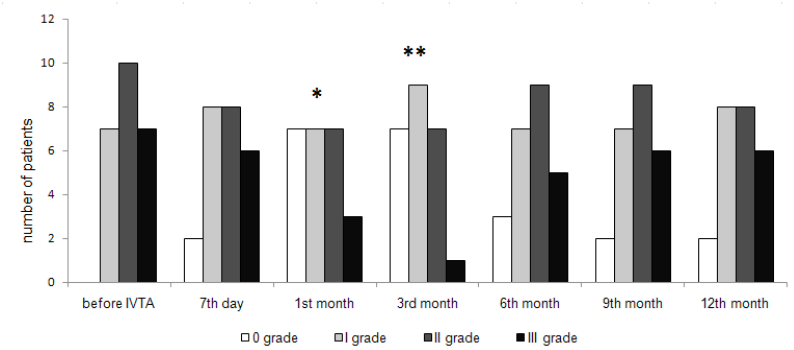

Figure 1. Grading the patients who received IVTA during a period of one year.

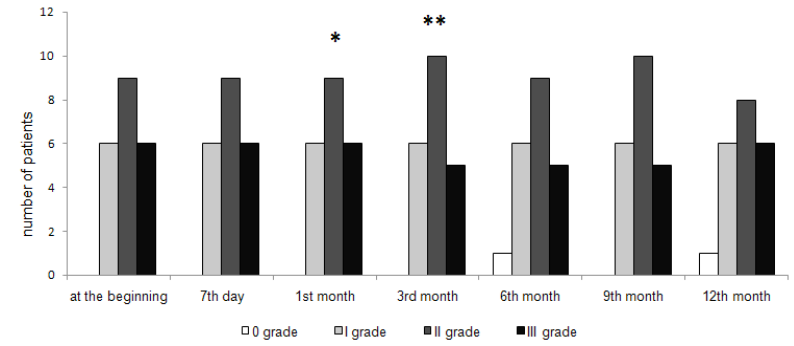

Figure 2. Grading the patients from the control group during a period of one year.

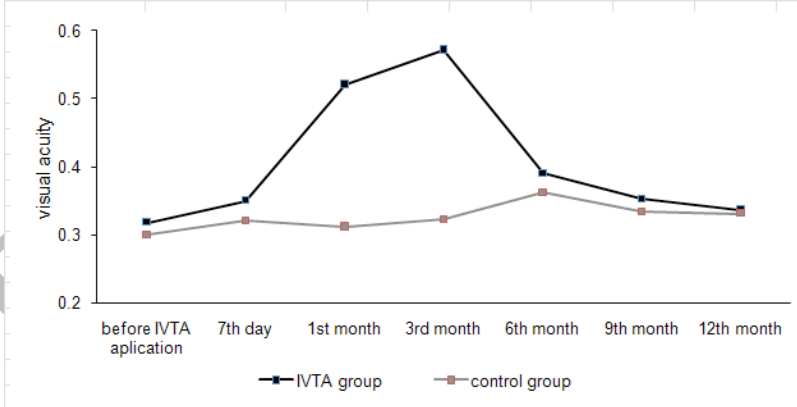

Figure 3. Comparison of visual acuity in patients who received TA and the patients from the control group.

Seven days after the IVTA application, no statistically significant differences were recorded in the density of vitreal hemorrhage (p=0.54) and the visual acuity (p=0.08).

At the third measurement, one month after the IVTA procedure, we detected for the first time, statistically significant difference. Twenty one patients divided equally in the first three grades and only one patient with severe vitreal hemorrhage were detected in the IVTA group. Comparing to the control group, where patients still were in the same schedule as they were at the beginning of the

study (0 grade – 0, I grade – 6, II grade – 9, III grade – 6) statistical significance was noticed ($p = 0.04$). That was followed by the improvement of visual acuity in the first group, 0.51 ± 0.08, while it remained the same in the second group, 0.34 ± 0.04. Again, we recorded statistically significant difference, $p=0.02$.

The statistically significant difference among the groups was captured three months after triamcinolone acetonide application, $p<0.05$; $p<0.001$. Both, vitreal hemorrhage and visual acuity were much better in those who received TA, then the patients from the control group ($p=0.01$; $p=0.001$).

The last three measurements, six, nine and twelve months after the administration of IVTA, passed without statistically significant difference ($p>0.05$). Vitreal hemorrhage and visual acuity were quite similar in both groups (Figures 1 & 3).

During this one year study, IOP measurements and detailed ophthalmological examinations were constantly performed. Three and six months after receiving triamcinolone acetonide, 7 patients (29.1%) had a temporary intraocular pressure rise, of over 5 mm Hg, than the IOP values they had before the triamcinolone acetonide injection. They were efficiently treated by appropriate antiglaucomatous medications - dorzolamide/timolol eye drops (®Cosopt, Laboratoires Merck Sharp & Dohme-Chibret, France) two times a day. One patient from the first group (4.1%) ended the study with the diagnosis of cataract. No endophthalmitis was recorded among those who underwent intravitreal application of triamcinolone acetonide.

DISCUSSION

The collagen fibrils and hyaluronic acid, contained inside the vitreal gel, are responsible for the integrity of the vitreal matrix. Fibrils are arranged as a fine network, with the glycosaminoglycans filling the gaps between them. When the hemorrhage in the vitreal cavity occurs, the polymorphonuclear neutrophils and macrophages get activated to phagocytize erythrocytes [9]. Intact erythrocytes leave the eye through the trabecular meshwork. Related to the slow vitreal lyses of fibrin, because of the low tissue fibrinolytic activity, elimination of the vitreal fibrin is also very slow (10). Despite the fact that erythrocytes leave the eye through the trabecular meshwork, intact blood cells can be histological detected in vitreal cavity many months after the accident. These erythrocytes provoke realizing of the macrophages' lysosomal enzymes, which by the process of the hemolysis, decompose them. The velocity of the vitreal hemorrhage reabsorption is approximately 1% per day [2]. The quantity of the vitreal hemorrhage as well as its occurrence frequency and the level of communication of the anterior and posterior segment of the eye determine the clearance rate [11]. Vitrectomy has an important role in the process of the vitreal hemorrhage clearing. Based on the reachable data, cleared vitreal cavity, after vitrectomy, expedites reabsorption of the remaining erythrocytes [12].

Corticosteroids can be useful for the treatment of retinal vascular and inflammation disorders by inhibition of different genes expression responsible for the synthesis of different mediators of inflammation and angiogenesis [13]. Intravitreally applied triamcinolone acetonide due to its low water solubility and its sustained crystal releasing, has prolonged action duration [12].

The real mechanism of the TA applied intravitreal on hemorrhage reabsorption is still not clear. TA crystals deposit along the retinal vasculature, making them look like frosted angiitis [14]. These phenomena make certain effects on the vitreal hemorrhage reabsorption. Despite the fact that PVD can be detected often in these eyes, rests of it persist along the retinal vasculature elements, and prolonged its action on the vascular elements [5]. By the mechanism of sedimentation of tramcinolone crystals with retinal blood elements and vascular stabilization, trimacinolone acetonide has its role in the cleaning of vitreal hemorrhage in the patients with proliferative diabetic retinopathy [15]. Using detailed ophthalmoscopic examination, we managed to identify those crystals, stationed along the retinal vasculatures, one month after the application of intravitreal TA (Figure 4). Based on our results, crystalshave remained for three months in the viteal cavity, which is in correlation with the improvement of the density of vitreal hemorrhage, and consequently with better visual acuity. After that period, crystals of the TA were not noticed in the vitreal cavity, and the results were quite similar to the control group. Temporary rise of the intraocular pressure, which was recorded in some patients three to six months after TA injection, indicated that triamcinolone was still present in the eye, even it wasn't identified during ophthalmological examination. That IOP rise was efficiently treated by locally applied medical therapy-antiglaucomatous eyedrops, without unwanted influence to the optic nerve, which was confirmed at the next control examination, three months later. Some studies reported much longer duration after the application of 20mg triamcinolone intravitreally [16,17]. Non existence of the unique opinion among the scientists, of the mechanism and duration of IVTA provides the new possibilities for future investigations.

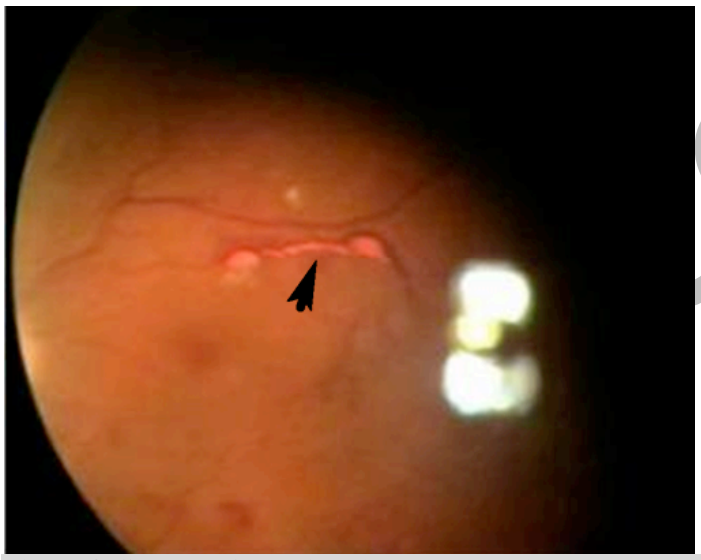

Figure 4. Crystals of the triamcinolone acetonide spotted one month after the intravitreal application of 20 mg TA.

CONCLUSION

Intravitreal application of the triamcinolone acetonide has a temporary and limited effect in the treatment of vitreal hemorrhage, followed by the transitory improvement of the visual acuity. TA can serve as the alternative therapy for the diabetic patients with massive vitreal hemorrhage, in those

cases where the vitrectomy is not recommended. Existence of the ocular comorbidities or contraindications for general anesthesia, such as abnormally high blood pressure, cardiopulmonary insufficiency, extreme obesity, senility, gives space for the usage of intravitreal triamcinolone acetonide. By this treatment we improve the patients' life quality for a while. Also, the intavitreal application can be repeated after a few months. Following the rules of sepsa and antisepsa as well as the guide for secondary glaucoma treatment, complication of this intervention can be decreased.

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