

Use of intravitreal bevacizumab or triamcinolone acetonide as a preoperative adjunct to vitrectomy for vitreous haemorrhage in diabetics

Injeção intravítrea de bevacizumabe ou triancinolona como adjuvantes da vitrectomia posterior no tratamento da hemorragia vítrea em diabéticos

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ABSTRACT

Purpose: To evaluate the effect of preoperative intravitreal bevacizumab (IVB) or triamcinolone (IVT) on the rate of early postvitrectomy hemorrhage in proliferative diabetic retinopathy (PDR). **Methods:** Eligible eyes were assigned randomly to 1 of 3 groups: the IVB group received 1.25 mg bevacizumab, the IVT group received 4,0mg triamcinolone and the control group underwent a sham procedure. The primary outcome measure was the incidence of early postvitrectomy hemorrhage. Secondary outcome measures included changes in visual acuity (BCVA) and adverse events. **Results:** Twenty and seven eyes, 9 in each group were randomized. The incidence of vitreous hemorrhage was lower in the IVB group ($p=0.18$). Postoperative vitreous hemorrhage at 1 month also was less in the IVB group compared with the control group ($p \geq 0.05$). The rate of bleeding immediately after surgery was higher in IVT group with 4 (44.4%) cases. The overall mean visual acuity was 1.72 ± 0.37 logMAR preoperatively and 1.32 ± 0.73 logMAR in 6 months after surgery. Assessing visual acuity by group evidenced that the IVB group had initial mean logMAR VA of 1.87 and 1.57 logMAR VA at the six months ($p = 0.84$). In IVT group, initial mean VA was 1.75 logMAR and 0.96 logMAR VA at six months ($p \leq 0.001$). And in control group, the initial mean VA was 1.85 logMAR and 1.57 logMAR VA at six months ($p= 0.34$). **Conclusion:** Intravitreal injection of bevacizumab 1 week before vitrectomy seems to reduce the incidence of early postvitrectomy hemorrhage in diabetic patients. There was a better visual acuity outcome in the triamcinolone group.

Keywords: Diabetic retinopathy/surgery; Vitrectomy; Angiogenesis inhibitors/therapeutic use; Triamcinolone/therapeutic use; Visual acuity

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RESUMO

Objetivo: Avaliar o efeito no pré-operatório da injeção intravítrea de bevacizumab (IVB) ou triamcinolona (IVT) sobre a taxa de hemorragia precoce pós-vitrectomia na retinopatia diabética proliferativa. **Métodos:** Os olhos foram distribuídos em três grupos: IVB - 1,25 mg bevacizumab, IVT - 4,0 mg de triamcinolona e o grupo controle - simulação da injeção. O objetivo primário foi a avaliação da incidência da hemorragia precoce pós-vitrectomia. Os objetivos secundários incluíram mudanças na acuidade visual corrigida e eventos adversos relacionados à injeção. **Resultados:** Dos Vinte e sete olhos, 9 foram randomizados em cada grupo. A incidência de hemorragia vítrea foi menor no grupo IVB ($P=0,18$). A hemorragia vítrea em 1 mês também foi menor no grupo IVB ($P \geq 0,05$). A taxa de sangramento pós-operatório imediato foi maior no grupo IVT com 4 (44,4%) dos casos. A média da acuidade visual (AV) foi de $1,72 \pm 0,37$ logMAR no pré-operatório e $1,32 \pm 0,73$ logMAR em 6 meses após a cirurgia. Analisando a AV por grupo evidenciamos que o grupo IVB tinha inicialmente AV média logMAR de 1,87 e AV logMAR de 1,57 em seis meses ($p = 0,84$). No grupo IVT, a média inicial de AV foi de 1,75 logMAR e 0,96 logMAR em seis meses ($p \leq 0,001$). E no grupo controle, a média inicial foi de 1,85 logMAR e 1,57 logMAR no seis meses ($p = 0,34$). **Conclusão:** A injeção intravítrea de bevacizumab antes da vitrectomia parece diminuir a incidência de hemorragia vítrea precoce pós-vitrectomia em diabéticos. Houve um melhor resultado na acuidade visual no grupo da triamcinolona.

Descritores: Retinopatia diabética/cirurgia; Vitrectomia; Inibidores da angiogênese/uso terapêutico; Bevacizumabe; Triamcinolona; Acuidade visual

INTRODUCTION

In spite of all the scientific advances in medicine and in our knowledge of the pathophysiology and treatment of diabetes over the past 25 years, diabetic retinopathy remains one of the leading causes of blindness in individuals between 20 to 64 years-old in industrialized countries^(1,2).

Proliferative diabetic retinopathy (PDR) is a major cause of visual loss in diabetic patients. In PDR, the growth of new vessels from the retina or optic nerve, is thought to occur as a result of vascular endothelial growth factor (VEGF) released into the vitreous cavity as a response to ischaemia⁽³⁻⁵⁾. Early postvitrectomy hemorrhage in diabetic patients is a major concern for both surgeons and patients. On the patient's side, expectations regarding visual improvement are not met, and this may be crucial in monocular patients. On the surgeon's side, this complication interferes with fundus examination, detection of iatrogenic retinal breaks, and performing laser therapy.

Because VEGF has been shown to play a major role in retinal neovascularization^(3,4), in conjunction with other factors^(6,7) anti-VEGF treatments have been hypothesized as an alternative adjunctive treatment for retinal neovascularization^(8,9).

To date, pars plana vitrectomy (PPV) is the treatment of choice for PDR with vitreous hemorrhage and retinal detachment. There is a high risk of complication due to the bleeding from fibrovascular membrane⁽¹⁰⁾.

Oral, topical and periocular steroids have been widely used in the past in many pathologic ocular conditions that have an underlying inflammatory basis. The retinal neovascular proliferation in PDR often has an accompanying inflammatory component. The intravitreal (IV) steroid injections, particularly triamcinolone acetonide, may potentially be important in quelling intraocular inflammation⁽¹¹⁻¹³⁾. It is therefore intuitive that IV steroid injections could be beneficial to PDR.

Bevacizumab (Avastin Genetech Inc., South San Francisco, California, USA) is a humanized anti-vascular endothelial growth factor (VEGF) antibody used for metastatic colorectal cancer. Recent reports have described the application of bevacizumab to treat ocular neovascular disorders including PDR⁽¹⁴⁻¹⁵⁾. Adjunctive use of intravitreal bevacizumab for severe PDR before vitrectomy has also been reported. However, the preferable timing from the injection to surgery has not been determined yet⁽¹⁶⁻¹⁸⁾.

The purpose of this study was to evaluate the efficacy of bevacizumab or triamcinolone acetonide intravitreal injections

as an adjuvant before vitrectomy surgery for vitreous haemorrhage in diabetic patients.

METHODS

The design of this study was an interventional consecutive, randomized prospective study. Twenty-seven patients (27 eyes) aged from 17 to 79 years old (mean age 52 years) with severe PDR and persistent Vitreous Hemorrhage (VH) for 6 months were enrolled and underwent PPV. Of the 27 enrolled patients, 9 underwent IV bevacizumab (1.25 mg in 0.05 ml) 5-7 days before PPV (IVB group), 9 underwent IV triamcinolone acetonide (4.0 mg in 0.1 ml) 5-7 days before PPV (IVT group) and 9 had surgery alone (control group). The patients were randomized in order to assign each study participant to group 1, 2 or 3. The main outcome measure was VH recurrences; a secondary goal was visual outcome at 6 months. The primary outcome measure was the incidence of early (<4 weeks) and late (>4 weeks) recurrent VH. Recurrent VH was defined as a new episode of grade 1 or more VH occurring 1 week after surgery.

Demographics and clinical findings, including age, gender, diabetes mellitus category and disease duration, blood glucose control, diabetes mellitus type, hypertension and renal disease anticoagulation were recorded. At baseline, each patient underwent detailed ophthalmologic examinations, including measurement of best-corrected visual acuity (BCVA) using EDTRS acuity test, slit-lamp biomicroscopic examination and indirect funduscopy examination when possible. Vitreous hemorrhage was evaluated by eye ultrasound. Post-surgery follow-up was scheduled at 1 week, 1 and 6 months. At each visit, complete ophthalmologic examinations were performed. The graduation of VH was done by indirect fundus examination using the classification above (clinical findings) and this findings evaluated by the score changes during the visits⁽¹⁹⁾.

Exclusion criteria were: tractional retinal detachment, tractional-rhegmatogenous retinal detachment, previous

Score	Description	Clinical findings
1	Minimal	Posterior pole clearly visible
2	Mild	Posterior pole details slightly haze
3	Moderate	Posterior pole details very haze
4	Marked	Posterior pole details barely visible
5	Severe	Fundal details not visible

vitrectomy in the study eye.

The procedure followed standard intravitreal injection protocol⁽¹⁹⁾. The surgical technique was the same for the groups. All patients underwent 20-gauge three-port PPV and further endolaser panretinal photocoagulation.

The study protocol adhered to the tenets of the Declaration of Helsinki. The off-label use of the drug and its potential risks and benefits were discussed extensively with all patients. All participants gave written informed consent before entering the study. Visual acuity measured in EDTRS was converted to logMAR for data analysis. Continuous variables were presented as mean and standard deviations (SD) and the Mann-Whitney test was performed. Non-parametric Friedman test was used to compare the evolution of mean VA. A significance level of 95% was considered statistically significant.

RESULTS

Of the 27 cases, nine were randomized to IVB group, nine to IVT group and nine to control group. The mean age of patients was 52.2 ± 13.9 years, 17 males and 10 females. The clinical characteristics of patients are shown in Table 1. There was no statistically significant difference between the clinical findings and visual acuity or recurrent VH.

The incidence of vitreous hemorrhage was lower in the IVB group 1 week after the operation ($p=0.18$). Postoperative

vitreous hemorrhage at 1 month also was no statistically significantly less in the IVB group compared with the control group ($p \geq 0.05$). The rate of bleeding immediately after surgery was higher in IVT group with 4 (44.4%) cases. There wasn't possible to calculate the relative risk for occurrence of any grade of vitreous hemorrhage in this sample.

The overall mean visual acuity was 1.72 ± 0.37 logMAR preoperatively and 1.32 ± 0.73 logMAR in 6 months after surgery, Figure 1. Assessing visual acuity by group evidenced that the bevacizumab group had initial mean logMAR VA of 1.87 and 1.57 logMAR VA at the six months, which was not statistically significant ($p = 0.84$). In IVT group, initial mean VA was 1.75 logMAR and 0.96 logMAR VA at six months, and this result was statistically significant ($p \leq 0.001$). And in control group, the initial mean VA was 1.85 logMAR and 1.57 logMAR VA at six months ($p = 0.34$), which was also not statistically significant.

There were no local complications (uveitis, infection or elevation of IOP) or systemic side effects (hypertension and thromboembolic events) after the injections or the surgeries.

DISCUSSION

Recurrent vitreous hemorrhage is one of the most common complications of vitrectomy in patients with diabetic retinopathy. Intravitreal bevacizumab injection is already performed for the

Table 1

Clinical characteristics of patients

Initials	Age	Sex	VA Pre	VA pos	Recurrent VH – (Score)	Time(days)	Type of DM	AAS	Insuline	Hb1ac	Creatinine
NT	82	F	1,9	1,2	-	-	2	No	No	6,1	1,7
OM	57	M	2,2	1,9	-	-	2	Yes	Yes	5,9	1,5
JRM	58	M	1,1	1,1	2	7	2	Yes	Yes	7	1,8
VS	56	M	2,2	1,9	-	-	2	Yes	Yes	5,5	1,5
LCS	58	M	2,2	1,9	-	-	2	No	Yes	7,1	1
RM	67	M	1,9	1,2	-	-	2	Yes	No	5,8	1,7
ISS	42	M	2,2	2,2	2	7	2	No	No	8,2	9
SB	48	F	1,6	1,6	-	-	2	Yes	Yes	6,8	2,3
MB	32	M	1,8	1,8	2	1	1	No	Yes	6,3	0,9
RF	41	M	1,9	1,4	-	-	2	No	Yes	7,3	1,1
ST	53	F	1,6	1,8	3	1	2	No	No	5,8	1,3
GA	27	F	1,8	1,4	1	7	1	Yes	Yes	6,2	1,1
ES	26	M	1,9	1,8	2	7	1	No	Yes	5,8	1,9
MMD	50	F	1,6	1,4	1	7	2	No	Yes	8,3	1
ES	26	M	1,8	1,8	1	1	1	No	Yes	5,8	1,9
GC	60	M	1,9	0,6	-	-	2	No	No	7	2
RF	41	M	1,6	1,6	3	14	2	No	Yes	7,3	1,3
CAM	51	M	1	0,6	-	-	1	Yes	Yes	7,2	1,6
WF	54	M	1,8	1,3	-	-	2	Yes	Yes	7,8	1,4
EIM	54	F	1,8	1,2	-	-	2	Yes	Yes	6,8	1,5
AL	60	F	2,2	1,3	-	-	2	No	No	7,1	1,4
FGB	66	F	1,8	1,8	1	14	2	No	No	6,7	2,3
MM	66	F	1,8	1,6	-	-	2	No	Yes	6,3	1,5
NGS	62	M	1,8	1,4	-	-	2	No	No	7,5	1,3
FDO	61	M	1	0,2	-	-	2	No	Yes	6,9	1,8
LF	67	M	0,9	0,9	1	7	2	Yes	Yes	8,8	2,0
NGV	65	F	1,6	1,4	-	-	2	Yes	Yes	8,7	1

VA = Visual acuity; VH = Vitreous Haemorrhage; DM = Diabetic Melitus; AAS = Acidum acetylsalicylicum

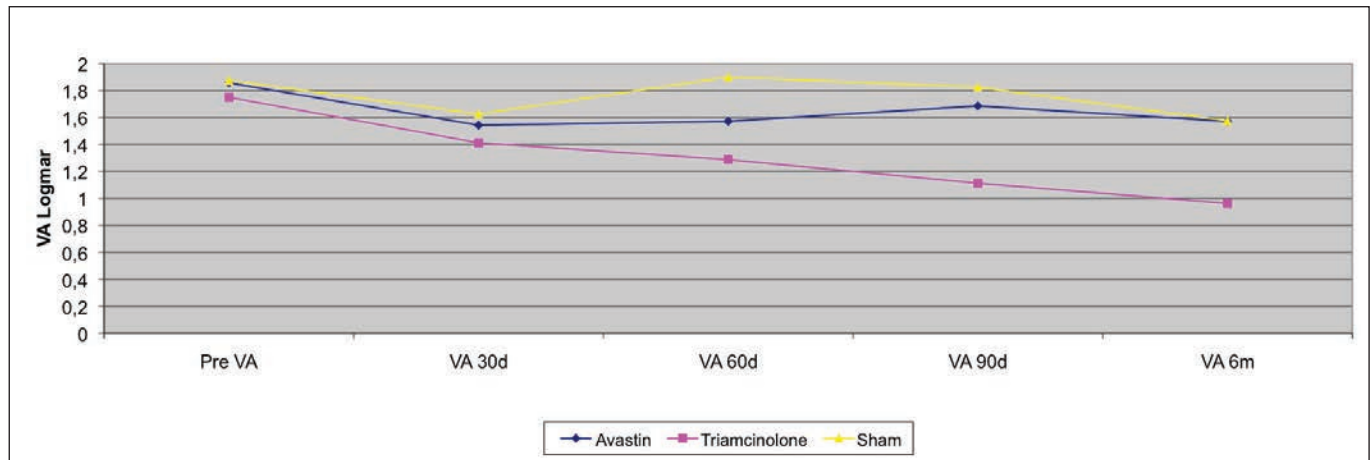


Figure 1: Visual acuity evolution

treatment of cystoid macular edema, membrane choroidal neovascularization and retinal neovascularization. Bevacizumab Injection induces rapid regression of neovascularization of the retina and iris in proliferative diabetic retinopathy⁽¹⁵⁻¹⁷⁾. Studies showed that patients who underwent bevacizumab in the end of vitrectomy had a lower rate of recurrent bleeding and reoperation⁽¹⁵⁾.

The preoperative injection of intravitreal bevacizumab may reduce intraoperative bleeding during dissection of membrane in PDR with tractional retinal detachment⁽¹⁷⁾. Intravitreal bevacizumab injection may not prevent postoperative VH, probably due to washing of bevacizumab during vitrectomy⁽²⁰⁾.

In this study, immediate postoperative VH occurred in 1 eyes in group 1, 4 eyes in group 2 and 8 eyes of the control group. But the rate of VH was not statistically significant between groups. The lower rate of re-bleeding in group 1 could be due to the theory in which bevacizumab helps to inhibit angiogenesis by reducing vascular endothelial growth factor (VEGF)⁽¹⁵⁻¹⁷⁾.

The exact mechanism by which bevacizumab reduces the incidence of immediate postoperative VH is unclear. Vascular Endothelial Growth Factor, the main factor in PDR, decreases significantly after bevacizumab injection and there is a rapid resolution of the neovascularization of the retina^(15,16). One possible mechanism is that this regression of neovascularization improves the integrity of the vessels retinal blood and therefore reduces the risk of postoperative bleeding⁽²¹⁻²³⁾.

The visual acuity in all groups showed improvement with 6 months follow-up. There are few studies that assessed visual acuity later than 6 months for patients who underwent bevacizumab before PPV. In IVB group the initial mean VA was 1.87 logMAR and it became 0.96 logMAR postoperatively.

In this study all groups had improvement in the visual acuity within 6 months postoperatively, but only in the group that underwent triamcinolone acetonide injection, this improvement was statistically significant ($p < 0.05$). Moreover, visual acuity improvement did not change between group control and IVB. These results are similar to that found by others authors⁽²¹⁻²⁴⁾. And there was a better visual acuity outcome in the triamcinolone group. We propose that the improvement in visual acuity in this group may be due to a progressive resolution of macular edema as triamcinolone's duration. It is worth noting that due to vitreous hemorrhage, macular edema was not evaluated preoperatively. Thus, there is the possibility of an underestimation of macular edema.

Intravitreal injection of bevacizumab 1 week before vitrectomy seems to reduce the incidence of early postvitrectomy hemorrhage in diabetic patients. The need for vitrectomy also may be decreased significantly in these cases.

The main weakness points in our study are the small sample size and the complexity of diabetic patients. Many of these patients had renal complications and uncontrolled diabetes that can contribute to an unfavorable outcome. Despite these limitations, the results observed in this series may encourage carrying out further studies to determine whether the use of bevacizumab or triamcinolone as a preoperative adjunctive to obtain success in vitrectomy for proliferative diabetic retinopathy.

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