SAFETY AND EFFICACY OF PREOP INTRAVITREAL TRIAMCINOLONE PLUS BEVACIZUMAB COMBINATION AND BEVACIZUMAB ALONE IN VITREOUS SURGERY FOR NON-RESOLVING VITREOUS HAEMORRHAGE IN PROLIFERATIVE DIABETIC RETINOPATHY (PDR)

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ABSTRACT

BACKGROUND

Diabetic retinopathy is much prevailing and contributing a major cause for visual morbidity, even a leading cause of total blindness among the people in their productive lifespan. Proliferative diabetic retinopathy is a major contributor to severe vision loss, very difficult to treat and requires complex surgical procedure. Here, we are suggesting our adjunctive procedure to standard diabetic vitrectomy to make the surgery little easier, shorter, safer and efficacious.

The aim of the study is to know the safety and efficacy of preoperative Intravitreal (IV) triamcinolone acetonide (2 mg) plus bevacizumab (1.25 mg) and intravitreal bevacizumab (1.25 mg) 3 days prior to the scheduled day of vitreous surgery in non-resolving vitreous haemorrhage in PDR.

MATERIALS AND METHODS

Prospective comparative study involving 28 PDR patients with non-resolving vitreous haemorrhage planned for surgery. Group 1 (n=15), IV triamcinolone acetonide (2 mg) + bevacizumab (1.25 mg) and group 2 (n=13) IV bevacizumab (1.25 mg). Preoperative Complexity Score (CS), surgical time, intraoperative manoeuvers, visual and anatomical outcome at 6 months observation.

RESULTS

CS was similar in both the groups (5.5) intraoperative bleeding grade 1 vs. 2, endodiathermy 2 vs. 5 and posterior vitreous detachment induction 2 vs. 5. Postoperative best corrected visual acuity improved more in group 1 than 2.

CONCLUSION

Safety and efficacy of preoperative IV triamcinolone + bevacizumab is better than IV bevacizumab alone in diabetic haemorrhage related vitreous surgery.

KEYWORDS

IV Triamcinolone, IV Bevacizumab, Non-Resolving Vitreous Haemorrhage in PDR, PVD Induction, Intraoperative Bleeding.

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BACKGROUND

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 Grow Factor (VEGF) released into the vitreous cavity as a response to ischaemia.[1-3] Approximately, 4.5% of patients with Proliferative Diabetic Retinopathy (PDR) require pars plana vitrectomy despite panretinal laser photocoagulation.[4] However, performing surgery in these patients is a challenging task especially when dealing with complications of PDR.

Bevacizumab (Avastin™, Genentech Inc., San Francisco, CA, USA) is a complete full-length humanised antibody that binds to all subtypes of VEGF and is successfully used in tumour therapy as a systemic drug.[5] Recent studies have demonstrated the usefulness of an intravitreal injection of bevacizumab in the reduction of vascular permeability and fibrovascular proliferation in macular oedema secondary to central vein occlusion, retinal neovascularisation secondary to PDR and choroidal neovascularisation secondary to age macular degeneration.[6-8] Intravitreal bevacizumab is also being tried for neovascular complications of proliferative diabetic

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retinopathy. There are many reports of intravitreal bevacizumab being well-tolerated and showing promising results in the treatment of PDR.[9,10]

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.[11,12] It is therefore intuitive that IV steroid injections could be beneficial to PDR.

This study aims to know the visual outcome of preoperative Intravitreal (IV) triamcinolone acetonide (2 mg) plus bevacizumab (1.25 mg) and intravitreal bevacizumab (1.25 mg) 3 days prior to the scheduled day of surgery in non-resolving vitreous haemorrhage in PDR.

MATERIALS AND METHODS

This study was an interventional, randomised and prospective study conducted in Ophthalmology Department, V.S.S. Institute of Medical Sciences and Research, Burla. 28 PDR patients (28 eyes) with non-resolving vitreous haemorrhage for 6 months were planned for PPV. Out of 28 patients, group 1 (n=15) underwent IV triamcinolone acetonide (2 mg) + bevacizumab (1.25 mg) and group 2 (n=13) IV bevacizumab (1.25 mg) 3 days prior to the surgery. These patients then underwent 23-gauge, 3-port vitrectomy, 3-4 days after the intravitreal injection. The main outcome measures were feasibility of the surgery and visual and anatomic outcome at 6 months.

Proper approval was taken from the ethical committee of the institute and informed consents were obtained from all the patients. The off-label use of the drug and its potential risks and benefits were discussed extensively with all patients. The patients with following conditions were excluded from the study- 1) History of previous vitrectomy in the study eye; 2) History of thromboembolic events; 3) Uncontrolled hypertension; 4) Those were on anticoagulants. 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 funduscopic examination when possible. Vitreous haemorrhage was evaluated by eye ultrasound.

To compare results among cases of similar complexity, Complexity Score (CS) developed by Grigorian, Castellarian et al[13] was used. The complexity score was graded by quantifying- 1) The number of quadrants of Fibrovascular Proliferation (FVP), 1-4 quadrants, each quadrant involved corresponds to a one point increase in the C. The location of FVP was also considered- if it was anterior to the equator, it corresponded to 0 points, if it was posterior to the equator, the score was 0 points; if FV spread both anteriorly and posteriorly, it scored 1 point. The presence of Tractional Retinal Detachment (TRD) scored 1 point, the presence of Tractional-Rhegmatogenous Retinal Detachment (TRRD) 2 points. Finally, the absence of posterior vitreous detachment was evaluated- if there was no PVD in the macular area, CS was increased by 1 point.

Group 1 received intravitreal injections of triamcinolone acetonide (2 mg) and 1.25 mg of bevacizumab, whereas group 2 received intravitreal injection of 1.25 mg of bevacizumab. All treatments were performed using peribulbar anaesthesia under sterile conditions. Intravitreal drugs were injected into the vitreous cavity using a 30-gauge needle inserted through the inferotemporal pars plana, 3.5 to 4 mm posterior to the limbus. Antiglaucoma and antibiotic drops were advised postoperatively. All patients underwent 23-gauge 3-port PPV, removal of epiretinal fibrovascular membranes, further endolaser panretinal photocoagulation and non-expansive C3F8 gas tamponed. The following parameters were recorded- Overall duration of the surgery, induction of posterior vitreous detachment, intraoperative bleeding and frequency of required endodiathermy. Intraoperative bleeding was divided into mild and severe. It was defined as grade 1, if stopped by increasing infusion pressure and/or by pressing with a blunt instrument and grade 2, if endodiathermy was required. After 6 months (BCVA), using EDTRS acuity test was noted and retinal thickness at macula was also measured using spectral domain OCT.

RESULTS

28 diabetic patients were enrolled in our study with the mean age of 57.2 years (range from 23 to 82 years). The patients' mean preoperative Complexity Score (CS) was 5.5 (ranging from 4.2 to 6.4) and was similar in the two groups. Intraoperative surgical records of both the groups has been discussed in Table 1.

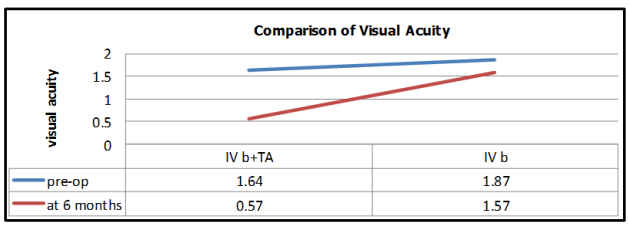
Parameters	Group 1 (n=15)	Group 2 (n=13)
Mean surgical time (minutes)	67	85
Intraoperative bleeding (grade)	1	2
Frequency of endodiathermy	2	5
Induction of PVD	2	5
Intraoperative retinal tears	0	2

Table 1. Intraoperative Surgical Record

The mean surgical time was shorter in group 1, 67 minutes (± 8) as compared to group 2 with a mean surgical time of 85 minutes (± 13). Intraoperative bleeding of grade 1, i.e. it stopped by increasing infusion pressure and/or by pressing with a blunt instrument in Group 1 compared to Group 2 where grade 2 intraoperative bleeding occurred, which was controlled by using endodiathermy. Endodiathermy had to be used twice in group 1 as compared to 5 times in group 2. During surgery, PVD had to be induced 2 times in group 1 as compared to 5 times in group 2. There was no intraoperative retinal tear in group 1, but it occurred 2 times in group 2.

Mean preoperative BCVA in the IV bevacizumab + triamcinolone group was 1.64 ± 0.42 LogMAR, which improved to 0.57 ± 0.25 LogMAR at 6 months follow-up postoperatively (p-value <0.001). The mean preoperative BCVA in the IV bevacizumab group was 1.87 ± 0.35

LogMAR, which improved to 1.57 ± 0.28 LogMAR postoperatively (p-value 0.84). The difference in the preoperative visual acuity in the 2 groups was not significantly different, but the difference in the postoperative visual acuity was statistically different.



Comparison of Visual Acuity

The mean central macular thickness in IV bevacizumab + triamcinolone group was 219 ± 161 µm and the mean thickness in IV bevacizumab group was 236 ± 164 µm. It is worth noting that due to vitreous haemorrhage, macular oedema was not evaluated preoperatively. Thus, there is the possibility of an underestimation of macular oedema.

DISCUSSION

Diabetic retinopathy is characterised by inflammation, including intravitreous induction of proinflammatory cytokine, intraretinal expression of proinflammatory caspases and mediators, and therefore, many clinical investigators have found that intravitreal injection of a corticosteroid like triamcinolone acetonide may reduce retinal oedema. Bevacizumab can induce regression of retinal neovascularisation in patients with diabetes; therefore, it was suggested that a presurgical administration of intravitreal bevacizumab may reduce intraoperative bleeding during vitrectomy in Proliferative Diabetic Retinopathy (PDR).[14] Combined effect of these two drugs has not yet been studied, so this study is a novel one trying to study the synergistic effect of these two drugs. In a study by Kriechbaum et al[15] (diabetic retinopathy research group), 3 injections of 2.5 mg bevacizumab and one 8 mg triamcinolone were compared. After 6 months, visual rehabilitation was comparable, but reduced in 12th month in triamcinolone group due to factors such as cataract formation. Our study shows a synergistic effect in group IVTA + IVB and which sustains till the end of the study.

The regression and subsequent fibrosis of retinal NV achieved after IVB + TA made the surgery quicker (67 vs. 85 minutes) as fewer tool exchanges were required. In this study, all groups had improvement in the visual acuity within 6 months postoperatively, but only in the group that underwent triamcinolone acetonide + bevacizumab injection, this improvement was statistically significant. These results are similar to that found by other authors[16-18] and there was a better visual acuity outcome in the triamcinolone group. We propose that the improvement in visual acuity in this group maybe due to a progressive resolution of macular oedema.

CONCLUSION

Thus, it is suggested that preoperative intravitreal bevacizumab + low dose (2 mg) triamcinolone acetonide is superior to preoperative intravitreal bevacizumab alone. The combination makes easy PVD induction, vitreous identification and lesser intraoperative bleeding. We have not considered cataract formation or progression in our study in combination of intravitreal bevacizumab + low dose (2 mg) triamcinolone acetonide group. Being our study is of lesser duration, use of low dose of steroid and the intravitreal retention of period of steroid is minimal as during vitrectomy procedure. The steroid was washed out or removed along with vitreous. These factors might have influenced our cataract progression and needs further study.

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