The Efficacy of Subconjunctival Bevacizumab in the Management of Rubeosis Iridis and Neovascular Glaucoma

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ABSTRACT

Objective: to compare the efficacy of Subconjunctival bevacizumab with intra vitreal bevacizumab in eyes with rubeosis iridis and neovascular glaucoma (NVG).

Method: a prospective study conducted at King Hussein Medical Centre and prince Rashid military hospital between December 2016 and June 2018. All eyes found to have rubeosis iridis or neovascular glaucoma were included in the study. Eyes with rubeosis iridis alone were divided randomly into 3 groups; group A are those which received intra vitreal 1.25 mg/0.05 ml bevacizumab, Group B are those which received subconjunctival injection of 3.75 mg /0.15 mL bevacizumab and Group C which did not receive bevacizumab. Eyes with NVG were divided randomly into two groups: those which received subconjunctival injection of 3.75 mg /0.15 mL bevacizumab upon starting IOP lowering agents (group D) and the remaining eyes received anti glaucoma medications without receiving the injection (group E). Eyes with NVG and scheduled for Ahmed glaucoma valve implant (AGV); half of them were randomly selected to receive subconjunctival injection of 3.75 mg /0.15 mL bevacizumab and the remaining eyes underwent surgery without the use of bevacizumab injection. All eyes underwent pan retinal photocoagulation (PRP). The eyes were assessed initially regarding best corrected visual acuity, level of intraocular pressure, degree of rubeosis at 2 weeks, 6 weeks and 3 months after treatment.

Results: Sixty patients (94 eyes) with a mean age of 57.1±8.2 years and male to female ratio of 3:2 were included in the study. The most commoncauses for rubeosis and NVG were diabetic retinopathy (67%) and retinal vein occlusion (16%). In eyes with rubeosis alone; at 3 months subconjunctival bevacizumab injection was able to induce regression of rubeosis in 77% of eyes compared with 82% in eyes with intravitreal injection and 62% in eyes that did not receive the injection. Eyes with NVG which received subconjunctival bevacizumab showed significant improvement in BCVA, more reduction in IOP, better regression of rubeosis and higher success rate Ahmed Glaucoma Valve (AGV) surgery.

Conclusion: Subconjunctival bevacizumab injection was effective as intravitreal route in treating the eyes with rubeosis. Eyes with neovascular glaucoma showed significant improvement in BCVA, more reduction in IOP, better regression of rubeosis and more success rate of AGV surgery.

Key words: neovascular glaucoma, rubeosis, subconjunctival bevacizumab.

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Introduction

Glaucoma is the 2nd leading cause of blindness after cataract. It is estimated that 67 million in the world have glaucoma and 6% of those patients are classified as secondary glaucoma.[1] Although the actual prevalence of neovascular glaucoma (NVG) is not well studied in Jordan but it is commonly seen during our practice at the ophthalmology clinic. Worldwide, NVG ranks the 5th cause of secondary glaucoma and accounts for 5% of secondary glaucoma cases.[2]

Rubeosis iridis occurs as a result of retinal ischemiacausing the release of vascular endothelial growth factors (VEGF) which will lead to the formation of fibrovascular membrane and prevent aqueous out flow from the anterior chamber resulting in elevated intraocular pressure and NVG.

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Clinical conditions commonly associated with retinal ischemia include; proliferative diabetic retinopathy, central retinal vein occlusion, and ocular ischemic syndrome. Other conditions like retinal artery occlusion, chronic retinal detachment, and intraocular malignancies were also reported to be a cause.[3]

The management of NVG includes lowering the IOP and treating the underlying cause. Pan retinal photocoagulation (PRP) is still the mainstay treatment of NVG; it can decrease the oxygen demand by destroying the outer photoreceptor–retinal pigment epithelium complex which is responsible for the majority of retinal oxygen consumption.[4] Surgical treatment of glaucoma is reserved for refractory cases.[5]

For the past few years Anti VEGF agents like bevacizumab were used in the management of NVG. It is usually given as intra vitreal injection and it showed to be effective during the period before the PRP effect take place.[6] However, intra vitreal injection may be associated with potential serious complication that may increase the risk of irreversible visual loss in the patients such as: endophthalmitis, vitreous hemorrhage, retinal detachment, and more increase in intra ocular pressure (IOP) which will cause further damage to the retinal nerve fiber layer.[7] Recently subconjunctival instead of intra vitreal bevacizumab was used in the management of NVG particularly prior to surgical intervention.[8]

The aim of this study is to evaluate the efficacy of Subconjunctival bevacizumab in eyes with rubeosis iridis and neovascular glaucoma in two tertiary military hospitals in Jordan.

Method

This is a prospective study conducted at King Hussein MedicalCentre and prince Rashid military hospital between December 2016 and June 2018. All eyes found to have rubeosis iridis or neovascular glaucoma were included in the study. Patients who underwent previous glaucoma surgery, patients with uncontrolled DM(HbA1C >8.0), patients who had intravitreal anti VEGF within last 3 months and those who had previous history of primary open angle glaucoma or secondary glaucoma not related to rubeosis were excluded from the study. Data was initially obtained from the patients regarding their age, gender and cause of NVG.

The patients with rubeosis iridis and normal IOP with no use of IOP lowering agents were divided randomly into 3 groups; group A are those who received intra vitreal 1.25 mg bevacizumab, Group B are those who receivedsubconjunctival injection of 3.75 mg /0.15 mL bevacizumab and Group C who did not receive bevacizumab.

On the other hand, the patients who had NVG were divided randomly into two groups: those who received subconjunctival injection of 3.75 mg /0.15 mL bevacizumab upon starting IOP lowering agents (group D), the remaining patients received anti glaucoma medications without receiving the injection (group E). For patients with NVG who were scheduled for Ahmed glaucoma valve implant (AGV); half of them were randomly selected to receive subconjunctival injection of 3.75 mg /0.15 mL bevacizumab and the remaining patients underwent surgery without the use of bevacizumab injection.Patients with NVG including those who were scheduled for surgery are already having uncontrolled elevated IOP and if they receive intra vitreal injection it may induce further increase in the IOP which may result in further damage to the optic nerve fibers

The patients were assessed initially regarding best corrected visual acuity, level of IOP, degree of rubeosis and were reassessed at two weeks, six weeks and three months after treatment.

Patients in all groups underwent pan retinal photocoagulation (PRP)of 2000-3000 shots over one to three sessions started immediately (group C,E,G) or one week post injection (groups A,B,D,F).

Ethical committee approval was granted before the start of the study. Simple statistical analysis such as mean, percentage, range and P value were used in the study.

Results

Sixty patients (94 eyes) were enrolled in the study. The mean age was 57.1±8.2 years with male to female ratio at 3:2. (Table I), represents the etiology found to be responsible for the development of rubeosis or NVG.

Table I: Etiology responsible for the development of rubeosis or NVG

Cause	Number of eyes (%)	Rubeosis only	NVG
Diabetic retinopathy	63 (67%)	40(63%)	23 (77%)
Retinal vein occlusion	15 (16%)	13 (20%)	2(7%)
Central	12 (80%)	10 (77%)	2 (100%)
Branch	2 (13%)	2 (15%)	0 (0%)
Hemispheric	1 (7%)	1 (8%)	0 (0%)
Uveitis	7 (8%)	5(12%)	2 (7%)
Chronic retinal	4 (4%)	3 (7%)	1 (3%)

detachment			
Ocular ischemic syndrome	2 (2%)	1 (2%)	1 (3%)
Endophthalmitis	2 (2%)	1(2%)	1 (7%)
Retinal artery occlusion	1 (1%)	1(2%)	0 (0%)
Total	94 (100%)	64 (100%)	30 (100%)

(Tale II) summarizes the eyes with rubeosis who received intravitreal (group A) or subconjunctival (group B) bevacizumab compared with those who did not receive the injection (group C).

Table II:

Patient's group	Group A (n=22)	Group B (n=21)	Group C (n=21)
Mean BCVA			
Base line	0.51	0.56	0.61
At 2 weeks	0.59	0.72	0.65
At 6 weeks	0.72	0.75	0.68
At 3months	0.79	0.77	0.68
Mean IOP (mmHg)			
Base line	16.1	15.9	16.5
At 2 weeks	18.5	16.1	16.4
At 6 weeks	16.0	15.7	15.9
At 3months	16.2	15.8	16.2
Rubeosis			
Base line	22(100%)	21(100%)	21(100%)
At 2 weeks	14(63%)	13 (67%)	18 (86%)
At 6 weeks	10((45%)	10 (48%)	13 (62%)
At 3months	4 (18%)	5 (23%)	8 (38%)

(Table III), represents the eyes with NVG who received sub subconjunctival injection of bevacizumab (group D) compared with those who did not receive bevacizumab injection (group E).

Table III:

Patient's group	Group D (n=12)	Group E (n=12)
Mean BCVA		
Base line	0.25	0.25
At 2 weeks	0.38	0.31
At 6 weeks	0.45	0.32
At 3months	0.56	0.32
Mean IOP (mmHg)		
Base line	35.2	32.5
At 2 weeks	23.1	24.2
At 6 weeks	16.0	21.2
At 3months	15.2	20.2
Rubeosis		
Base line	12(100%)	12(100%)
At 2 weeks	9(75%)	10 (83%)
At 6 weeks	6(50%)	8 (67%)
At 3months	2 (17%)	3 (33%)
Number of medications (anti glaucoma eye drops)		
Base line	0	0
At 2 weeks	1.5	2.5
At 6 weeks	1.9	3.2
At 3months	1.9	3.7

(Table IV), represents the eyes with NVG who received subconjunctival bevacizumab (group F) immediately before performing (AGV) surgery compared with those who underwent the operation without the injection (group E).

Table IV:

Patient's group	Group F (n=3)	Group G (n=3)
Mean BCVA		
Base line	0.13	0.16
At 2 weeks	0.17	0.16
At 6 weeks	0.25	0.25
At 3months	0.33	0.25
Mean IOP (mmHg)		
Base line	42.1	39.2
At 2 weeks	24.2	29.5
At 6 weeks	17.0	21.6
At 3months	17.2	22.6
Rubeosis		
Base line	3(100%)	3 (100%)
At 2 weeks	2(67%)	3 (100%)
At 6 weeks	1(33%)	2 (67%)
At 3months	1 (33%)	2(67%)

Intra vitreal hemorrhage was seen in 3 patients and endophthalmitis was seen in one patient among eyes which received intra vitreal injection. While subconjunctival hemorrhage was seen in two patients who received the injection subconjunctivally.

Discussion

NVG is still one of the challenging conditions seen at the ophthalmology clinic because of lack of effective IOP control which can improve or prevent visual deterioration despite a variety of medical and surgical treatment options. In this study eyes with rubeosis iridis with or without glaucoma were reviewed. There was no statistical significant difference between the two groups regarding age and gender. This condition was more common in males than females at a ratio of 3:2.

The most common cause for rubeosis was diabetic retinopathy (67%) and retinal vein occlusion (16%). Those results were in line with previous studies conducted worldwide but with variable percentages and sometimes variable order. For example, in USA Hoskins found that diabetic retinopathy was the most common cause for rubeosis at a rate of 33% followed by retinal vein occlusion (28%) while Brown found the later to be the most common etiology at 36.1% compared to diabetic retinopathy at 32.2%.[9,10] In China and Saudi Arabia diabetic retinopathy was responsible for rubeosis in 39.7% and 56.1% respectively.[11,12] Compared to those studies diabetic retinopathy was responsible for rubeosis at much higher rate which is most probably attributed to the higher prevalence of diabetes and diabetic retinopathy among Jordanian population compared with other populations.[13,14]Diabetic retinopathy was found at higher rate (77%) among patients with NVG than those with rubeosis alone, this may be explained by the fact that glaucoma and higher IOP is more prevalent in diabetic patients even without rubeosis.[15,16] Unlike other studies, uveitis was the 3rd cause of rubeosis and NVG at a rate of (8%) which could be attributed to the geographical variation regarding prevalence of uveitis among Jordanian population compared with other populations.[17] It should be mentioned that all the bilateral cases of rubeosis were caused by diabetic retinopathy. In addition, diabetes was found in all patients with retinal vein occlusions causing NVG and in 77% of those patients with rubeosis alone. Therefore, effective glycemic control can greatly minimize the risk of diabetic retinopathy and subsequent rubeosis and NVG.

Bevacizumab (avastin) was successfully used to treat rubeosis which can be introduced to the eye by intra vitreal, intra cameral or sub conjuctival injection.[18,19,20] In this study there was no significant difference between the eyes that received bevacizumab either intra vitreal or subconjunctival routes and those who did not receive the injection regarding the base line BCVA and IOP. On follow up at two weeks , six weeks and three months the results showed no statistical significant difference between those groups but with slight more improvement in eyes which received the intra vitreal injection compared with the eyes which did not; this might be due to improvement of diabetic retinopathy and possible associated diabetic macular edema among diabetic patients induced by bevacizumab.[21] At two weeks there was a regression of rubeosis in 37% in patients who received

intra vitreal bevacizumab with comparable but slightly lesser extent in patients who received sub conjuctival injection (33%) while laser a lone was much less effective in promotingrubeosis regression at a rate of 14%.. At 6 weeks and three months intra vitreal injection continued to be superior (55%% & 82%) to subconjunctival injection (52% & 77%) in inducing rubeosis regression but with no statistical significance (P value>0.05). On the other hand in eyes that did not receive the injection the rates were (14%, 38% and 62%) at two weeks, six weeks and three months respectively.The results suggest that subconjunctival bevacizumab was very close in efficacy for promoting rubeosis regression to intravitreal route. Nomoto et al reported that bevacizumab was found at lower but effective concentrations in the iris/ ciliary body of rabbit eyes when given subconjunctival compared with intravitreal route. Furthermore, Nomoto also found that the concentration of bevacizumab concentration is maintained in the iris for 10.3 and 8.4 weeks when administered intravitreal or subconjunctival routes respectively.[23] By this time the effect of PRP is expected to take place which will cause destruction of the ischemic retina responsible for VEGFs release that was the primary factor responsible for the development of rubeosis. Some studies reported that anti VEGF may still be effective in the human eyes for up to 12 weeks.[24]Sub conjuctival bevacizumab will bind to scleral tissue forming a depot which may sustain the release and diffusion of the drug into the iris tissues.This all may explain the favorable outcome achieved at three month post injection.

Eyes with NVG which received subconjunctival bevacizumab (group D) showed significant improvement in BCVA at two weeks, six weeks and three months compared with eyes with PRP alone (group E).Despite the baseline mean IOP was higher in group D but at three months the mean IOPwas significantly lower than that in eyes with group E. (Figure 1) shows the percentages of IOP reduction at those times in both groups.

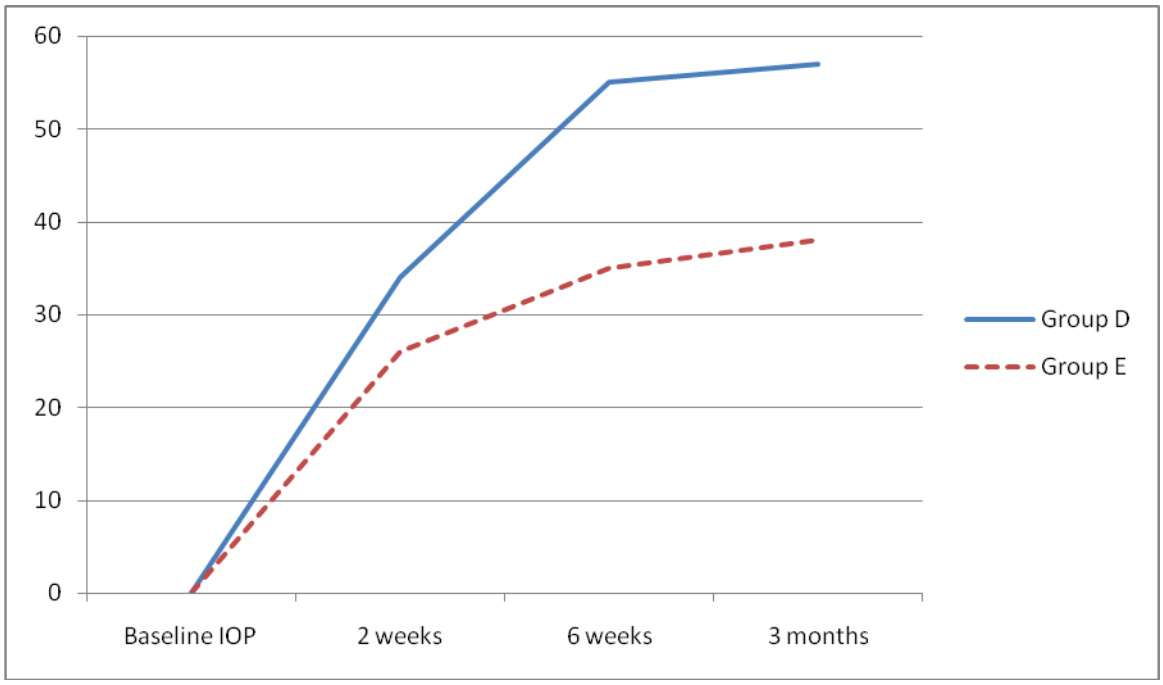

Fig1: The percentage of IOP reduction from the baseline at two weeks, six weeks and three months

Those results showed that subconjunctival injection of bevacizumab induced lower IOP when combined with PRP. Ehlers et al found similar results but by using intravitreal injection rather than subconjunctival approach.[25] This suggests that the efficacy of subconjunctival bevacizumab is comparable to that of intravitreal route in eyes with NVG. An additional advantage of giving the anti VEGF subconjunctival instead of intravitreal is that we avoid temporal increase in the IOP after intravitreal injection which may be harmful to optic nerve and the retina in patients with NVG.The efficacy of subconjunctival bevacizumab on rubeosis in eyes with NVG was similar to that in eyes without NVG. The number of anti-glaucoma medications also was significantly lower in eyes received combined subconjunctival bevacizumab/PRP than those with PRP alone. This will positively influence the patient's compliance to the medications and decrease its financial impacts.

Patients with NVG and scheduled for AGV surgery showed significant improvement in BCVA, more reduction in IOP and better regression of rubeosis in patients when given subconjunctival bevacizumab. If Hang criteria is used to assess the success rate of AGV surgery it will be clearly shown that the success rate was significantly higher among eyes which received the injection. Taking in consideration the relatively low success rate of AGV surgery in eyes with NVG.[26,27]

Although the relatively small number of eyes involved in the study and the short term follow up, the above results showed that subconjunctival bevacizumab injection was almost as effective as intravitreal route in treating the eyes with rubeosis which will help in avoiding serious complication like retinal detachment, vitreous hemorrhage and endophthalmitis.[28,29,30] Further studies are needed to explore the efficacy of subconjunctival bevacizumab in eyes with retinal neovascularization. In addition, subconjunctival bevacizumab showed promising results in treating the eyeswith NVG and it has a positive impact on the success rate of AGV surgery.

Conclusion

Subconjunctival bevacizumab injection was effective as intravitreal route in treating the eyes with rubeosis. Eyes with neovascular glaucoma showed significant improvement in BCVA, more reduction in IOP, better regression of rubeosis and more success rate of AGV surgery.

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