Ophthalmology Research: An International Journal
3(4): 129-135, 2015, Article no.OR.2015.018
ISSN: 2321-7227

SCIENCEDOMAIN *international*
www.sciencedomain.org

Repeated Intravitreal Bevacizumab Injections versus Single Combined Intravitreal Bevacizumab and Posterior Subtenon Triamcinolone Injections for Treatment of Diabetic Macular Edema

Amin F. Ellakwa[1], Sameh S. Mandour[1*] and Nermeen M. Badawi[1]

[1]Department of Ophthalmology, Faculty of Medicine, Menoufia University, Shebin El Kom, Menoufia, Egypt.

Authors' contributions

This work was carried out in collaboration between all authors. The surgical procedures were done by all authors. Author AFE designed the study, wrote the protocol. Author SSM wrote the manuscript and managed the literature searches and author NMB made the statistical analysis of the data. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/OR/2015/15827
Editor(s):
(1) Tatsuya Mimura, Department of Ophthalmology, Tokyo Women's Medical University Medical Center East, Japan.
Reviewers:
(1) Mitzy E. Torres Soriano, Retina Department, Centro Medico Cagua, Venezuela.
(2) Otzem Chassid, Bar Ilan University, Israel.
(3) Anonymous, Japan.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=890&id=23&aid=7943

Original Research Article

Received 20th December 2014
Accepted 14th January 2015
Published 29th January 2015

ABSTRACT

Aim: To compare efficacy of combined intravitreal bevacizumab and subtenon triamcinolone versus three intravitreal injections of bevacizumab at one month interval for reducing foveal thickness.
Methods: Sixty eyes of 30 diabetic patients with bilateral diabetic macular edema were randomly enrolled in two groups, group A eyes treated with three intravitreal injections of Bevacizumab of 1 month apart, and group B eyes treated with a single intravitreal injection of Bevacizumab combined with a subtenon triamcinolone in the same operative session. Pre and postoperative clinical data were measured and followed up over 6 months.
Results: Difference between pre-treatment and post-treatment clinical data for each parameter in the same group was highly statistically significant. However, on comparing results of post treatment BCVA, IOP and CMT in both groups, there was no statistically significant difference.
Conclusion: Combination of subtenon triamcinolone and intravitreal bevacizumab is a safe and effective choice to treat DME.

**Corresponding author: E-mail: dr_ssmandour@hotmail.com;*

Keywords: Intravitreal; subtenon; bevacizumab; triamcinolone; macular edema.

1. INTRODUCTION

Diabetic macular edema (DME) is the most common cause of vision loss in diabetic patients [1]. Grid laser photocoagulation was proved effective in reducing progressive visual loss in clinically significant macular edema. However, the laser scar may enlarge postoperatively reducing visual acuity afterwards [2,3].

Recently, it was found that both intravitreal concentrations of interleukin-6 (IL-6), (an inflammatory cytokine) and vascular endothelial growth factor (VEGF), (a cytokine related with vascular proliferation and hyper-permeability) were increased in DME [4,5] and many reports indicate that intravitreal or posterior subtenon triamcinolone acetonide (TA) treatment is effective for reducing macular thickness in DME [6-9]. More recently, an intravitreal injection of bevacizumab, a full-length humanized monoclonal anti-VEGF antibody, has been reported to be also effective in reducing DME [10,11]. As well, variable combinations of the fore mentioned manoeuvres were used to augment the effect of each other and proved effective.

The aims of this study were to compare the efficacy of single combined intravitreal injection of bevacizumab (IVB) and posterior subtenon triamcinolone (PSTA) versus three intravitreal injection of bevacizumab at one month interval for reducing foveal thickness, and to evaluate the visual prognosis and effect on intraocular pressure over a 6 months follow up period.

2. PATIENTS AND METHODS

This is a prospective, randomized clinical study that was conducted on 60 eyes of 30 diabetic patients (type 2 DM) with bilateral diffuse DME, whose foveal thickness was ≥ 250 μm and best corrected visual acuity (BCVA) worse than 0.4 (Snellen's fraction). The eyes were randomly enrolled in two groups, group A eyes that were treated with three intravitreal injections of Bevacizumab of 1 month apart, and group B eyes that were treated with a single intravitreal injection of Bevacizumab combined with a subtenon injection of triamcinolone on the same operative session. After randomization, the two eyes of the same patient received only one type of treatment.

Exclusion criteria included patients who had previous therapies for macular edema, including grid-laser treatment, intravitreal injection of any drugs, and/or vitreous surgery. As well, we excluded patients with diabetic papillopathy, ischemic maculopathy with capillary nonperfusion, and any other ocular diseases such as glaucoma, retinal vessel occlusion, uveitis, or other ocular inflammatory/neovascular diseases. Furthermore, an eye was considered ineligible if OCT suggested that vitreoretinal interface disease (e.g., vitreoretinal traction, epiretinal membrane) was the primary cause of the macular edema.

After explaining to the patients the purpose of the study and the possible outcomes, an informed consent was obtained prior to the interventions. This study was approved by the clinical research committee of the Menoufia University Hospital and it followed the tenets of Declaration of Helsinki.

All patients received a comprehensive ocular examination before, during and after treatment. BCVA was determined with the Snellen chart (converted to Snellen fraction), intraocular pressure (IOP) was measured with Goldmann applanation tonometer, retinal thickness including central macular thickness (CMT), was measured by optical coherence tomography (OCT) (Zeiss-Humphrey, spectral domain, Dublin, California, USA) before treatment and during the follow-up examinations. A macular thickness map was made from six radial scans that intersected at the fovea using the OCT retinal mapping program (version 6.2). This program calculates mean thickness in nine regions: the 1000-μm central area, and the four quadrants of the inner and outer rings. The diameters of the inner and outer rings were 1000 μm to 3000 μm and 3000 μm to 6000 μm, respectively.

Indirect ophthalmoscopy and slit-lamp biomicroscopy of the posterior segment using a Volk Superfield contact lens (Volk, Mentor, Ohio, USA) were performed by at least two of the three authors to establish the presence of DME. Fundus photographs were taken at appropriate times. An intravenous fluorescein angiography (IVFA) was performed to detect and assess diffuse leakage around the fovea and to rule out macular ischemia.

Experimental Design: According to the previous reports [11-13] and our clinical experiences, the

concentration of each drug was determined as follows. In each patient of group A, 1.25 mg of bevacizumab (Avastin; Genetech, Inc, South San Francisco, California, USA) was injected into the vitreous at each injection setting. Three intravitreal injections were given separated by 1 month. In group B, 4 mg of triamcinolone acetonide (Kenacort; Bristol-Myers Squibb, Tokyo, Japan) was injected in the subtenon space of the affected eye. At the time of the drug injection, topical anesthesia was induced by applying 0.5% proparacaine topical anesthetic drops at least three times. Following disinfection and draping, in group A, in each injection setting, 0.05 ml volume containing 1.25 mg of bevacizumab was injected into the vitreous cavity using a sharp 30 gauge-needle at a distance of 3.5 mm from the limbus. In group B, the same was done as in group A in addition to injecting 1.0 mL of a 40 mg/mL dosage of triamcinolone acetonide in the inferotemporal quadrant using a 27-gauge needle on a 1-mL syringe. In both groups, to avoid an increase of IOP, aqueous humor was removed by paracentesis as appropriate.

Statistical analysis was performed using the SPSS statistical program (SPSS Inc., Chicago, IL, USA). Serial comparison of pre treatment and post treatment main outcome measures was evaluated using the paired Student t test. A p value less than 0.05 was considered statistically significant.

3. RESULTS

A total of 60 eyes of 30 patients were recruited and randomly enrolled into 2 groups. Group A included 8 males and 7 females ranging in age from 50 to 71 years with a mean of 58.93±6.47 (± SD) years. Group B included 7 males and 8 females ranging in age from 45 to 75 years with a mean of 56.4±8.09 (± SD) years.

Table 1 demonstrates the pre and post-treatment clinical data of patients of group A which included BCVA (expressed as Snellen's fraction), CMT (in µm) and IOP (in mmHg). The same data for patients of group B are presented in Table 2. These data were collected for every patient in both groups before starting treatment as well as in the postoperative follow up period at 1, 3 and 6 month duration. The difference between pre-treatment and post-treatment measurements for each parameter in the same group was highly statistically significant.

There was no statistically significant difference between both groups regarding pre-treatment clinical data. As well, on comparing the results of post treatment impact on BCVA, CMT and IOP in both groups, there was no statistically significant difference as shown in Table 3.

During the follow up period, there were no significant postoperative complications in both groups apart from one case in group A and 2 cases in group B who had an IOP elevation of more than 5 mmHg than preoperative. No cataract, infection, retinal detachment, vitreous hemorrhage or retinal complications was recorded in any case of the study.

Table 1. Pre and post-treatment clinical data of patients of group A

Group A n=30	Pre-treatment	Post-treatment			P value*
		1 month	3 months	6 months	
BCVA (fraction)	0.20±0.13	0.24±0.15	0.33±0.17	0.36±0.18	0.001
CMT (µm)	466.87±154.07	429.27±137.53	373.47±127.38	329.73±118.79	0.001
IOP (mmHg)	15.73±3.20	17.60±2.82	15.93±2.39	14.87±2.28	0.001

** Friedman test*

Table 2. Pre and post-treatment clinical data of patients of group B

Group B n=30	Pre-treatment	Post-treatment			P value*
		1 month	3 months	6 months	
BCVA (fraction)	0.18±0.11	0.21±0.11	0.29±0.16	0.31±0.15	0.001
CMT (µm)	496.13±137.67	454.87±123.98	386.73±111.62	361.60±103.61	0.001
IOP (mmHg)	15.53±2.29	17.60±1.81	15.93±2.64	15.00±1.78	0.001

** Friedman test*

Table 3. Comparison between both groups regarding clinical data before and after treatment

		Group A	Group B	P value*
Pre-treatment	BCVA	0.20±0.13	0.18±0.11	0.488
	CMT	466.87±154.07	496.13±137.67	0.857
	IOP	15.73±3.20	15.53±2.29	0.391
1 month after treatment	BCVA	0.24±0.15	0.21±0.11	0.627
	CMT	429.27±137.53	454.87±123.98	0.458
	IOP	17.60±2.82	17.60±1.81	0.928
3 months after treatment	BCVA	0.33±0.17	0.29±0.16	0.449
	CMT	373.47±127.38	386.73±111.62	0.700
	IOP	15.93±2.39	15.93±2.64	0.929
6 months after treatment	BCVA	0.36±0.18	0.31±0.15	0.224
	CMT	329.73±118.79	361.60±103.61	0.225
	IOP	14.87±2.28	15.00±1.78	0.564

** Mann Whitney U test*

4. DISCUSSION

DME has been attributed to intravitreous induction of proinflammatory cytokine [4], intraretinal expression of proinflammatory caspases [14] and mediators [15], and therefore, many clinical investigators have found that intravitreal injection of triamcinolone acetonide (IVTA) may reduce macular edema. Although the reduction effect of triamcinolone on macular edema improves visual functions, recurrence of macular edema was often observed within 24 weeks after treatment [7], and IOP was occasionally increased in this therapy.

Therefore, looking for safer and longer-acting therapy for DME was going on. VEGF has been shown to be an endothelial cell-specific mitogen and an angiogenic inducer, and is also known as a vascular permeability factor, which has been demonstrated to increase retinal vessel permeability by increasing the phosphorylation of tight junction proteins [16]. Since it was reported that the vitreous level of VEGF increased and correlated with the severity of macular edema in DME patients [5], anti-VEGF therapy is expected to show a dramatic reduction of DME.

However, the pathogenesis of DME is likely to be more closely related to a corticosteroid sensitive mechanism than a VEGF-dependent one. Corticosteroid affects a number of different cytokine including VEGF [17], thus it may be necessary to reduce more than one cytokine to make an effective reduction in DME. Therefore, at least theoretically, combining bevacizumab with triamcinolone would be expected to induce augmented reduction of CMT and improvement of BCVA than use of bevacizumab alone.

Intravitreal injection of anti-VEGF has a short term effect on DME and multiple injections are required to ensure relatively longer period of improvement. A regimen of three intravitreal injection of bevacizumab one month apart was proved effective in reduction of DME and improvement of visual acuity. We adopted this regimen for treatment of patients of group A in the current study and we observed marked improvement of DME which was statistically significant as compared by preoperative data without significant increase in the IOP.

Intravitreal injection, although an effective way of drug delivery to the vitreo-retinal complex, has its own dangerous complications such as endophthalmitis, vitreous hemorrhage and retinal detachment. The incidence of these complications increases as the frequency of injections increases. In the current study we compared the effect of three consecutive intravitreal injection of bevacizumab versus a single intravitreal injection of bevacizumab combined with the less dangerous subtenon injection of triamcinolone.

Posterior Subtenon Triamcinolone (PSTA), as an adjunctive treatment for diffuse DME, can improve the visual outcomes of laser photocoagulation [18-20]. As well, some reports suggest the beneficial effects of subtenon or peribulbar steroid injection therapy for DME [21,22]. In a study done by Bakri and Kaiser, visual acuities remained stable or improved over a 12-month period after PSTA injections for refractory DME in 63 eyes of 50 patients. Complications were rare, with a transient significant rise in intraocular pressure at the 3-months' evaluation as well as occurrence of ptosis in two patients [21].

Many reports compared the results of intravitreal versus subtenon injection of triamcinolone for DME and found no significant difference between both. Özdek et al. [22] showed that both PSTA and IVTA injections caused a significant increase in visual acuity and a decrease in central foveal thickness, especially in the short term. The effect was more pronounced in the IVTA group; however, PSTA injection also seemed to be a safe and effective technique for the treatment of DME [22].

An advantage of posterior subtenon administration is the lower risk of complication. IOP elevation is the most common complication after IVTA [23,24]. Although not statistically significant, IOP after intravitreal injection tended to rise in a study done by Choi et al. [25] At 3 months after injection, the change of IOP in the intravitreal injection group was greater than that of the posterior subtenon injection group. They concluded that the short-term efficacy of the intravitreal injection and of the posterior subtenon injection of triamcinolone in diffuse diabetic macular edema was similar. The posterior subtenon injection was less invasive and safer than the intravitreal injection [25].

Another study done by Cellini et al. [26] went farther in favouring PSTA to IVTA. They demonstrated that three months after IVTA and PSTA there is a statistically significant improvement in visual acuity and an equally significant reduction in retinal thickness. Six months after IVTA the patients presented a recurrence of macular edema with loss of visual acuity whereas six months after SBT injection, retinal thickness and visual acuity remained stable. After one, three and six months they observed a statistically significant rise of the IOP in the eyes treated with IVT injection whereas in the SBT injection group, no statistically significant variations of the IOP were found. However, none of patients developed cataract or needed anti-glaucoma drugs during the follow-up [26].

Based on the efficacy proposed for subtenon TA in management of DME, we combined it with a single intravitreal injection of bevacizumab for the treatment plane in group B in the current study. Visual acuity and CMT were significantly reduced over the 6 months follow up period. We thought that subtenon TA has a remarkable effect on prolongation of the improvement induced by the intravitreal injection of bevacizumab. There were no statistically significant differences between the results of both groups in the current study at 1, 3 and 6 months during the follow up period. However, the absolute values of VA and CMT may be better in group A.

As well, no significant increase in IOP was observed in patients of group B supporting the weak effect of subtenon TA on IOP compared with intravitreal TA. Moreoverl, no cataract has been reported to be induced by subtenon TA in patients of group B during the 6 months follow up period. However, longer follow up time may be needed to report occurrence of cataract in those cases.

4. CONCLUSION

We conclude that the combination of subtenon TA and intravitreal bevacizumab is a safe and effective choice to treat DME avoiding the multiple intravitreal injections with its potential dangerous complications. Meanwhile, we used TA, which is more effective in reducing DME, in a safer way minimizing the risk of postoperative glaucoma and cataract reported with its intravitreal use. An Additive effect is thus supposed to exist when using both TA and bevacizumab for treatment of DME. However, it is a relatively short term study and more follow up period is needed to confirm the long term effect of both modalities of treatment on the ocular structure.

ETHICAL APPROVAL

Authors have obtained all necessary ethical approval from the institutional Committee. After explaining to the patients the purpose of the study and the possible outcomes, an informed consent was obtained prior to the interventions. This study was approved by the clinical research committee of the Menoufia University Hospital and it followed the tenets of Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Moss SE, Klein R, Klein BEK. The incidence of visual loss in a diabetic population. Ophthalmology. 1988;95:1340-1348.

2. Early treatment diabetic retinopathy study research group. Photocoagulation for diabetic macular edema, Report No. 1. Arch Ophthalmol. 1985;103:1796-1806.
3. Early treatment diabetic retinopathy study research group. Focal photocoagulation treatment of diabetic macular edema, Report No. 19. Arch Ophthalmol. 1995;113:1144-1155.
4. Funatsu H, Yamashita H, Ikeda T, Mimura T, Eguchi S, Hori S. Vitreous levels of interleukin-6 and vascular endothelial growth factor are related to diabetic macular edema. Ophthalmology. 2003;110:1690-1696.
5. Funatsu H, Yamashita H, Sakata K, et al. Vitreous levels of vascular endothelial growth factor and intracellular adhesion molecule 1 are related to diabetic macular edema. Ophthalmology. 2005;112:806–816.
6. Sutter FK, Simpson JM, Gilles MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: Three month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. Ophthalmology. 2004;111:2044 – 2049.
7. Massin P, Andren F, Haouchine B, et al. Intravitreal triamcinolone acetonide for diabetic macular edema-Preliminary results of a prospective controlled trial. Ophthalmology. 2004;111:218-225.
8. Martidis A, Duker JS, Greenberg PB, et al. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology. 2002;109:920–927.
9. Verma LK, Vivek MB, Kumar A, Tewari HK, Venkatesh P. A prospective controlled trial to evaluate the adjunctive role of posterior subtenon triamcinolone in the treatment of diffuse diabetic macular edema. J Ocular Pharmacol Ther. 2004;20:277–284.
10. Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, et al. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema. Ophthalmology. 2007;114:743–750.
11. Haritoglou C, Kook D, Neubauer A, et al. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. Retina. 2006;26:999–1005.
12. Entezari M, Ahmadieh H, Dehghan MH, et al. Posterior sub-tenon triamcinolone for refractory diabetic macular edema: A randomized clinical trial. Eur J Ophthalmol. 2005;15:746-50.
13. Cardillo JA, Melo Jr LAS, Costa RA, Skaf M, Belfort Jr R, Souza-Filho AA, Farah ME, Kuppermann BD. Comparison of intravitreal versus posterior sub-Tenon's capsule injection of triamcinolone acetonide for diffuse diabetic macular edema. Ophthalmology. 2005;112:1557-1563.
14. Mohr S, Xi X, Tang J, Kern TS. Caspase activation in retinas of diabetic and galactosemic mice and diabetic patients. Diabetes. 2002;51:1172-1179.
15. Joussen AM, Murata T, Tsujikawa A, Kirchhof B, Ursel SE, Adamis AP. Leukocyte-mediated endothelial cell injury and death in the diabetic retina. Am J Pathol. 2001;158:147–152.
16. Ferrara N. Vascular endothelial growth factor: Basic science and clinical progress. Endocr Rev. 2004;25:581–611.
17. Barnes PJ. Corticosteroid effects on cell signaling. Eur Respir J. 2006;27:413–426.
18. Verma LK, Vivek MB, Kumar A, et al. A prospective controlled trial to evaluate the adjunctive role of posterior subtenon triamcinolone in the treatment of diffuse diabetic macular edema. J Ocul Pharmacol Ther. 2004;20:277-284.
19. Shimura M, Nakazawa T, Yasuda K, et al. Pretreatment of posterior subtenon injection of triamcinolone acetonide has beneficial effects for grid pattern photocoagulation against diffuse diabetic macular oedema. Br J Ophthalmol. 2007;91:449-454.
20. Tunc M, Onder HI, Kaya M. Posterior sub-Tenon’s capsule triamcinolone injection combined with focal laser photocoagulation for diabetic macular edema. Ophthalmology. 2005;112:1086-1091.
21. Bakri SJ, Kaiser PK. Posterior subtenon triamcinolone acetonide for refractory diabetic macular edema. Am J Ophthalmol. 2005;139:290-4
22. Ozdek S, Bahceci UA, Gurelik G, Hasanreisoglu B. Posterior subtenon and intravitreal triamcinolone acetonide for diabetic macular edema. Journal of Diabetes and its Complications. 2006;20:246-251.
23. Jonas JB, Degenring RF, Kreissig I, et al. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. Ophthalmology. 2005;112:593–598.

24. Smithen LM, Ober MD, Maranan L, et al. Intravitreal triamcinolone acetonide and intraocular pressure. Am J Ophthalmol. 2004;138:740-743.
25. Choi YJ, Oh IK, Oh JR, Huh K. Intravitreal versus posterior subtenon injection of triamcinolone acetonide for diabetic macular edema. Korean J Ophthalmol. 2006;20:205-209.
26. Cellini M, Pazzaglia A, Zamparini E, Leonetti P, Campos EC. Intravitreal vs. subtenon triamcinolone acetonide for the treatment of diabetic cystoid macular edema. BMC Ophthalmol. 2008;8:5.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=890&id=23&aid=7943