Advanced Pharmaceutical Bulletin

Adv Pharm Bull, 2014, 4(4), 375-378
doi: 10.5681/apb.2014.055
http://apb.tbzmed.ac.ir

Research Article

Effect of Adding Oral Calcium Dobesilate to Laser Photocoagulation on the Macular Thickness in Patients with Diabetic Macular Edema: A Randomized Clinical Trial

Mostafa Feghhi[1], Fereydoun Farrahi[1], Mohammadreza Abbaspour[2]*, Akbar Takhtaeian[1]

[1] *Infectious Ophthalmic Research Center, Department of Ophthalmology, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*

[2] *Nanotechnology Research Center, Department of Pharmaceutics, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*

Article info

Article History:
Received: 20 February 2014
Revised: 22 April 2014
Accepted: 23 April 2014
ePublished: 10 August 2014

Keywords:
· Calcium dobesilate (Doxium)
· Clinically significant macular edema (CSME)
· Macular thickness
· Diabetic retinopathy
· Macular photocoagulation (MPC)

Abstract

Purpose: To evaluate the effect of oral calcium dobesilate (Doxium) on macular thickness in clinically significant macular edema (CSME).

Methods: Overall, 71 eyes of 40 patients with non-proliferative diabetic retinopathy and clinically significant macular edema were included. All patients were received laser treatment for macular edema. Coherence optical tomography was used to determine the retinal thickness. Patients were randomized into two groups: group A received three Doxium capsule daily and group B received three placebo capsule daily for six months.

Results: The mean macular thickness before and after treatment in the group A was 340 and 257 micrometers respectively (24.5% reduced), and in the group B was 336 micrometers and 263 micrometers respectively (21.5% reduced). Macular thickness significantly decreased after treatment in both groups and the reduction in group A is higher but the difference of reduction between the two groups was not statistically significant (P>0.05).

Conclusion: In respect to the effect of adding oral Doxium to Laser Photocoagulation on the macular thickness in patients with diabetic macular edema, this study showed no statistically significant difference between Doxium and placebo.

Introduction

Diabetes Mellitus (DM) is a metabolic disorder of the body, in which either a sufficient amount of insulin in the body does not exist or the existing insulin may not perform his task properly.[1] Diabetic retinopathy (DR), the most important ocular complication in patients with DM is the leading cause of blindness in patients aged 20-65 years in the United States and in individuals between the ages of 30 and 64 in the United Kingdom; in which, it accounts for nearly 12%–14% of new cases of blindness resulting from all causes.[2-5] Retinal edema threatening or involving the macula is an important visual outcome of abnormal retinal vascular permeability in DR. The diabetic macular edema (DME) is diagnosed by slit-lamp biomicroscopy of the posterior pole. DME is caused by a breakdown in the blood-retinal barrier that lead to the accumulation of fluid in the space between the layers of retina in the macular area.[5] Data from the Early Treatment Diabetic Retinopathy Study (ETDRS) showed that focal laser photocoagulation of clinically significant diabetic macular edema (CSME) substantially reduces the risk of visual loss. Focal treatment also increases the chance of visual improvement, decreases the frequency of persistent macular edema, and causes only minor visual field losses. Therefore the presence or the absence of the CSME is the most important and the only specific factor defining the need to the treatment.[6] Laser treatment prevents vision loss, but does not have a significant effect on improving vision. This problem evokes the researchers for alternative therapies. The use of intravitreal injection of the steroid compound in some studies has reported good results.[7,8] Also intravitreal injection of the Bevacizumab (Avastin) has showed good results.[9] Calcium dobesilate (Doxium) is an anti-oxidative and angio-protective drug that decreases edema by regulating and improvement the physiological function. Recent studies have shown that Doxium is a potent antioxidant, particularly against the highly damaging hydroxyl radical. In addition, it improves diabetic endothelial dysfunction, reduces apoptosis, and slows vascular cell proliferation.[10,11] Doxium recently remains the object of interest in treatment of diabetic retinopathy, but various results have been reported by different studies performed on reducing the macular edema by Doxium.[11-14] Thus, this study was conducted to assess the effect of oral Doxium adding to macular laser

***Corresponding author:** Mohammadreza Abbaspour, Tel/Fax: +98 611 3738381; Email: abbaspourmr@ajums.ac.ir

photocoagulation on the macular thickness in patients with CSME.

Materials and Methods

Study design and population

A randomized, single blinded, placebo-controlled trial was conducted on patients with type II DM that had diabetic retinopathy and referred to the ophthalmology clinic, Imam Khomeini Hospital, Ahvaz, Iran from 2012-07-22 to 2013-01-19. The IRCT registration number of the study was: IRCT2012091610852N1.

Inclusion criteria

All patients with non-proliferative diabetic retinopathy and CSME which at least have 20/200 visual acuity were included.

Exclusion criteria

Patients with the history of previous treatment for a CSME such as macular laser and intravitreal injection of Avastin, posterior segment trauma, the need for the further eye surgery such as vitreo-retinal surgery or cataract, cases of non-feasible clinical observation, optical coherence tomography (OCT) and *fluorescein angiography (*FA) such as severe opacities of the media, the existence of a previous vascular pathology of the retina or age-related macular degeneration, a history of previous intraocular surgery, visual acuity less than 20/200 and presence of macular ischemia in FA were excluded.

Intervention

The demographic profile of patients includes age, gender, occupation, history of DM and smoking, were collected. Then, visual acuity of the patients was measured using the Snellen chart. Patients were examined with a Slit-Lamp (Topcon; Tokyo Optical Co., Ltd., Tokyo, Japan) and fundoscopy was done with the Volk's 78D and 90D lenses. Intraocular pressure (IOP, mmHg) was measured using a Goldmann applanation tonometer. FA (Topcon; Tokyo Optical Co., Ltd., Tokyo, Japan) of the retina was performed for all patients to monitor the areas of leakage and the macular thickness was measured using OCT (Topcon; Tokyo Optical Co., Ltd., Tokyo, Japan). Then the patients by simple randomization were divided into two groups, group A; receiving three capsules of Doxium 500 milligram daily and group B; receiving three capsules of placebo (containing starch with same sizes and color as Doxium capsules) daily for six-month. All patients were received classic laser treatment for macular edema, and six-month later again undergone the OCT to measure the macular thickness. Macular laser therapy was performed based on the ETDRS chart and algorithm using standard protocol with green laser set up every laser point with 50 to 100 micrometers. The emission duration was 0.1 second and the power was set right with the proper laser lighting effect, and the area of the macula has exposed, so that at least 500 micrometers from the edge of the optic disk and 500 micrometers away from the center of fovea. The laser energy was started at 50 mV and gradually increased until a modest and proper white spot revealed in the macula.

Outcome

Primary outcome; macular thickness

Secondary outcomes: visual acuity and intraocular pressure

Statistical analysis

After gathering information, data were analyzed by SPSS 19.0. Descriptive statistics (mean and standard deviation) were used to describe the desired variables. Then to determine the relationship between the variable T-test and paired T-test and ANOVA were used. Significant level was considered equal or lesser than 0.05.

Results

Overall, 40 patients (mean age of 53.55 ± 8.8, rang of 36-72 years) were studied, which 22 patients (55%) were male and 18 patients (45%) were female. There was no significant difference between groups A and B in term of age (54 ± 9.5 vs. 53.1 ± 9.8, respectively). In this study, total of 71 eyes were studied (36 eyes in group A and 35 eyes in group B), that 33 (46.5%) and 38(53.5%) were the right and left eyes respectively. In both groups after treatment the macular thickness reduced so that in group A the reduction was 80 micrometers (24.5%) and in the group B it was 75 micrometers (21.5%). The difference of changes in the macular thickness between the two groups was not statistically significant (Table 1). Six months after treatment, nine-eye (25%) in groups A and ten-eye (28.5%) in groups B need laser retreatment. The difference between the two groups was not statistically significant. The difference of visual acuity increase and the change of the mean IOP before and after treatment had no statistically significant difference between the two groups (Table 1).

Table 1. Comparing the variables of interest before and after treatment with oral Doxium and macular laser

Variables	Before treatment (Mean ± SD)			After treatment (Mean ± SD)		
	Group A	Group B	P-value	Group A	Group B	P-value
Macular thickness, µm	340.8 ± 85.46	336.05 ± 81.27	0.81	257.44 ± 55.04	263.34 ± 66.62	0.68
Visual acuity, Log Mar	0.595 ± 0.192	0.567 ± 0.199	0.54	0.509 ± 0.166	0.495 ± 0.213	0.76
IOP, mmHg	13.52 ± 1.44	13.91 ± 1.59	0.28	13.00 ± 1.37	13.25 ± 1.55	0.40

Discussion

Diabetic maculopathy is one of the most important causes of vision loss among people around the world today. Though laser photocoagulation remains as the gold standard therapy for diabetic macular edema, only a slight visual improvement has been reported following laser therapy. Therefore, different methods of treatment besides laser therapy are used to treat DME more effectively. In this study we assessed the effect of adding oral Doxium to macular photocagulation on the macular thickness in patients with DME. In many studies the effect of Doxium on the DR has been reviewed, but the effect of this drug on the macular thickness was less evaluated. In the present study reducing macular edema evaluated with macular thickness measurement using the OCT as a more accurate method. In most studies the effect of Doxium on DR investigated and none of the studies has considered the macular thickness using OCT.

Rota et al. studied the effect of Doxium on the retinal albumin leakage in streptozotocin-diabetic rats for 10 days, and suggested that this drug stabilizes blood-retinal barrier in diabetic retinopathy.[12] Haritoglou et al. investigated the effect of Doxium in the diabetic patients with mild-to-moderate non-proliferative diabetic retinopathy, and reported that this drug did not reduce the risk of development of CSME.[13] Our study was in line with Haritoglou et al. study and revealed that Doxium didn't reduce the diabetic macular edema, but the difference was the same as our study. We measured the macular thickness using OCT before and after treatment but Haritoglou et al. just studied the effect of Doxium in terms of the risk of progression of clinical significant macular edema.

Fesharaki and Modaresi, measured the effect of Doxium on the visual acuity and surface area of retinal hemorrhage in patients with non-proliferative diabetic retinopathy, and claimed that this drug (250 mg two tablets per day for six months) may has a positive effect on visual activity.[14] In contrast with Fesharaki and Modaresi, in our study, Doxium has no effect on the visual improvement of the patients.

Ribeiro et al. studied the effect of Doxium on the blood-retinal barrier (BRB) permeability in early diabetic retinopathy, and showed that the dosage of two grams of this drug daily for two-year has a significantly better activity on prevention of BRB disruption, with a very good tolerance.[15]

Vojnikovic studied the effect of oral Doxium on the 79 non-insulin-dependent diabetic subjects with early retinopathy and open-angle glaucoma, and suggested that this drug reduces blood hyperviscosity and lowers IOP, with a beneficial effect on retinal state and visual fields.[16] Our study revealed the oral Doxium has no effect on IOP; of course we excluded the patients with a history of glaucoma and high IOP, and only the effect of this drug on the IOP of diabetic patients without a history of glaucoma were evaluated.

Stamper et al. evaluates the efficacy of Doxium for treating non-proliferative diabetic retinopathy by clinical examination, FA and fundus photography and failed to demonstrate any beneficial effect of Doxium.[17]

Conclusion

Doxium has no statistically significant effect on macular thickness, visual acuity and intraocular pressure in patients with DME treating by macular laser photocoagulation.

One of the advantages of the present study was the quantitative observation of the macular thickness using OCT as a more accurate method. But the major weaknesses in our study were the short follow-up period, the high cost of supplying the drug, and no observation of the effect of the drug on the systemic blood sugar levels. Further studies in the longer follow-up period and larger sample size are recommended.

Ethical Issues

This study was approved by the ethics committee of Ahvaz Jundishapur University of Medical Sciences (ETH-469) and informed consent was obtained from all patients.

Acknowledgements

This study was the thesis of Dr. A. Takhtaeian and supported by a grant from vice chancellor for research, Ahvaz Jundishapur University of Medical Sciences (U-91033).

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Powers AC. Diabetes Mellitus. In: Longo DL, Fauci AS, Kasper DL, Stephen LH, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2012. P. 2968-70.
2. Ferris FL, 3rd, Patz A. Macular edema. A complication of diabetic retinopathy. *Surv Ophthalmol* 1984;28 Suppl:452-61.
3. Patz A, Smith RE. The ETDRS and Diabetes 2000. *Ophthalmology* 1991;98(5 Suppl):739-40.
4. Ghafour IM, Allan D, Foulds WS. Common causes of blindness and visual handicap in the west of Scotland. *Br J Ophthalmol* 1983;67(4):209-13.
5. Skuta GL, Cantor LB, Weiss JS. Retina and Vitreous disease. San Fransisco: American Academy of Ophthalmology; 2011-2012.
6. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol* 1985;103(12):1796-806.
7. Bonini-Filho MA, Jorge R, Barbosa JC, Calucci D, Cardillo JA, Costa RA. Intravitreal injection versus sub-Tenon's infusion of triamcinolone acetonide for refractory diabetic macular edema: a randomized clinical trial. *Invest Ophthalmol Vis Sci* 2005;46(10):3845-9.

8. Jonas JB, Sofker A. Intraocular injection of crystalline cortisone as adjunctive treatment of diabetic macular edema. *Am J Ophthalmol* 2001;132(3):425-7.
9. Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, Sanchez JG, Wu L, Maia M, et al. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. *Ophthalmology* 2007;114(4):743-50.
10. Allain H, Ramelet AA, Polard E, Bentue-Ferrer D. Safety of calcium dobesilate in chronic venous disease, diabetic retinopathy and haemorrhoids. *Drug Saf* 2004;27(9):649-60.
11. Garay RP, Hannaert P, Chiavaroli C. Calcium dobesilate in the treatment of diabetic retinopathy. *Treat Endocrinol* 2005;4(4):221-32.
12. Rota R, Chiavaroli C, Garay RP, Hannaert P. Reduction of retinal albumin leakage by the antioxidant calcium dobesilate in streptozotocin-diabetic rats. *Eur J Pharmacol* 2004;495(2-3):217-24.
13. Haritoglou C, Gerss J, Sauerland C, Kampik A, Ulbig MW, Group CS. Effect of calcium dobesilate on occurrence of diabetic macular oedema (CALDIRET study): randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2009;373(9672):1364-71.
14. Fesharaki H, Modaresi H. The effect of calcium dobesilate on non-prolifrative diabetic retinopathy. *J Isfahan Med Sch* 2003;21(68):5-10.
15. Ribeiro ML, Seres AI, Carneiro AM, Stur M, Zourdani A, Caillon P, et al. Effect of calcium dobesilate on progression of early diabetic retinopathy: a randomised double-blind study. *Graefes Arch Clin Exp Ophthalmol* 2006;244(12):1591-600.
16. Vojnikovic B. Doxium (calcium dobesilate) reduces blood hyperviscosity and lowers elevated intraocular pressure in patients with diabetic retinopathy and glaucoma. *Ophthalmic Res* 1991;23(1):12-20.
17. Stamper RL, Smith ME, Aronson SB, Cavender JC, Cleasby GW, Fung WE, et al. The effect of calcium dobesilate on nonproliferative diabetic retinopathy: a controlled study. *Ophthalmology* 1978;85(6):594-606.