The Effect of Macular Laser Photocoagulation on Visual Prognosis Before and After Intravitreal Triamcinolone Acetonide Injection in Diabetic Macular Edema

Diyabetik Makula Ödeminde, Vitre İçi Triamsinolon Asetonid Enjeksiyonundan Önce veya Sonra Yapılan Makuler Lazer Fotokoagülasyonun Görme Prognozuna Etkisi

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Geliş Tarihi/*Received:* 30.06.2014
Kabul Tarihi/*Accepted:* 13.11.2014

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ABSTRACT Objective: To investigate the effect of macular laser photocoagulation (PC) on visual acuity (VA) before and after intravitreal triamcinolone acetonide (IVTA) injection in patients with diabetic macular edema (DME). **Material and Methods:** A hundred and thirty-four eyes that received single-dose IVTA 4 mg following DME diagnosis were divided into three groups: eyes with no PC (n=37), eyes that received PC before IVTA 8n=46) and eyes that received PC only after IVTA (n=51). Visual acuity values (LogMAR) were measured at start (before injection), 1. week, 1st, 3rd and 6th months, 1st and 2nd year for comparisons. **Results:** DME cases who received macular PC and then IVTA showed significant improvements in VA at 1st week (p=0.008) and 1st, 3rd, 6th months (p=0.001, p=0.002, p=0.001 respectively) when compared to pre-treatment value. Patients who received only IVTA showed significant VA improvement at 6th month (p=0.001). Patients who received IVTA and then macular laser PC in the first month showed similar VA results when compared to patients who received only IVTA. During the two years follow-up, 4% of all patients developed secondary glaucoma that was controlled by medication. **Conclusion:** In patients with DME, IVTA injection with or without macular laser PC provided significant improvement in VA of all eyes during six months. IVTA combined with macular laser PC treatment in the 1st month did not provide an additional benefit. However, we suggest that it may be useful for reducing VA loss at the end of two years.

Key Words: Intravitreal injections; macular edema; triamcinolone acetonide; visual acuity

ÖZET Amaç: Diyabetik makula ödemli (DMÖ) olgularda, vitre içi triamsinolon asetonid (İVTA) enjeksiyonundan önce veya sonra makuler lazer fotokoagülasyon (FK) yapılmasının görme keskinliği (GK) üzerine olan etkisini araştırmak. **Gereç ve Yöntemler:** DMÖ tanısı ile tek doz 4 mg İVTA uygulanmış 134 göz, hiç makuler FK yapılmamış olanlar (37 göz), yalnızca İVTA öncesi makuler FK yapılmış olanlar (46 göz) ve yalnızca İVTA sonrası makuler FK yapılmış olanlar (51 göz) olmak üzere 3 gruba ayrıldı. Hastaların enjeksiyon öncesi, 1. hafta, 1. ay, 3. ay 6. ay, 1. yıl ve 2. yılda GK değerleri (LogMAR) karşılaştırıldı. **Bulgular:** Öncesinde makuler FK yapılmış olan DMÖ'lü olgularda İVTA sonrası 1. hafta (p=0,008) ve 1. ay, 3. ay ve 6. ayda (p=0,001, p=0,002, p=0,001) başlangıca göre GK'de anlamlı artış saptanmıştır. DMÖ tanısı ile sadece İVTA yapılan olgularda GK 6. ayda, başlangıca göre anlamlı derecede daha iyidir (p=0,001). İVTA sonrası 1. ayda makuler lazer FK yapılan olgularla, sadece İVTA yapılan olgular arasında GK değerleri benzer olarak saptanmıştır. İki yılda olguların %4'ünde medikasyonla kontrol altına alınabilen sekonder glokom gelişmiştir. **Sonuç:** DMÖ'lü olgularda, İVTA enjeksiyonu ile beraber makuler lazer FK yapılan ve yapılmayan bütün gözlerde GK'de 6 ay boyunca anlamlı artış sağlandığını saptadık ve İVTA ile kombine 1. ayda uygulanan makuler lazer tedavisinin, sadece İVTA uygulamasına göre ilk bir yıl boyunca ek bir kazanım sağlamamakla beraber, iki yıl sonunda gelişebilecek GK kaybını azaltmakta faydalı olabileceğini düşündük.

Anahtar Kelimeler: İntravitreal enjeksiyon; makula ödemi; triamsinolon asetonid; görme keskinliği

doi: 10.5336/ophthal.2014-41243

Turkiye Klinikleri J Ophthalmol 2015;24(1):22-8

Diabetic retinopathy (DR) is the most common chronic complication of diabetes. In developed countries, it is the leading cause of blindness between 20-74 years of age. It has been found that nearly 28% of patients who have diabetes longer than twenty years develop diabetic macular edema (DME).[1] Nearly 50% of patients with DME lost at least two lines visual acuity (VA) in the following two years.

The primary treatment with proven efficacy in DME is laser photocoagulation (PC). In clinically significant macular edema (CSME) and diffuse DME, macular laser PC is performed as focal or grid treatments.[2] The aim of laser treatment is to protect visual level. Only 15% of the treated eyes showed VA improvement. Grid laser treatment significantly reduces DME after 3-6 months. Focal DME responds laser treatment better than diffuse macular edema. It has been reported that focal macular PC in the treatment of DME decreased moderate visual loss 50% at the end of three years, but only 3% of the patients showed 15 letters increase in VA.[3,4]

Corticosteroids can be used in various eye diseases as topical, systemic, periocular or intravitreal injections. Triamcinolone acetonide that is used in the treatment of DME is a synthetic, crystallized corticosteroid and non-soluble in water.[5] Intravitreal triamcinolone acetonide (IVTA) reduces macular edema by decreasing VEGF (a vascular permeability factor) production, improving tight junctions of endothelial cells and stabilizing inner blood-retina barrier.[6-8]

In the treatment of laser unresponsive (resistant) diffuse DME, VA results of IVTA were various. Some studies reported insignificant increases at 1st and 3rd months, whereas others reported significant differences in the 2nd month and insignificant differences in the 4th month.[9,10] Some studies reported significant results in 1 and 3. months, and insignificant results in 6. month.[11-13] And finally some studies reported significant results even at the 6. month.[14,15] Previously, IVTA was considered as an alternative in resistant DME cases, but now some authors suggest it as a first choice treatment without combination.[16,17] Macular PC performed after IVTA was reported to provide significant VA increases at 3rd and 6th months, whereas some studies reported insignificant differences.[18-21] There are few studies evaluated the effects of macular PC added to IVTA on VA. This study was planned to investigate the effects of macular laser PC combined with IVTA on visual prognosis in DME.

MATERIAL AND METHODS

STUDY GROUP

In this retrospective study, patients with DME who received 4 mg IVTA treatment and followed up between April 2004 and March 2010 were investigated. Exclusion criteria included any ocular disease except DR, any intravitreal injection before IVTA, glaucoma or intra ocular pressure (IOP) higher than 20 mmHg, IVTA injections with a different dose, non-intact posterior capsule before IVTA, IVTA combined with cataract surgery. Patients who did not attend follow-up visits were also excluded. Study protocol was approved by local ethics committee (Approval code: TÜTFEK 2010/11; date: 09.07.2010).

Best-corrected visual acuity (BCVA) values of the patients were obtained by Snellen's board and transformed into "Logarithm of Minimum Angle of Resolution (LogMAR)" scale. Anterior segment biomicroscopy was performed, and IOP was measured by Goldmann applanation tonometry. A detailed fundus examination was done by using 78 Dioptre non-contact lens after pupil dilatation by 1% tropicamide gutt. Before IVTA treatment, all patients underwent Fundus Fluoressein angiography (FFA) to document DME. Retinal thickening that smaller than the two optic disc diameter size was accepted focal DME. Retinal thickening which including foveal center and two or more optic disc diameter sized was accepted diffuse DME.[22] We treated diffuse DME and focal DME which meet the CSME criteria according to Early Treatment Diabetic Retinopathy Study (ETDRS) report.[2]

FFA was repeated during follow-up when needed. Angiographic examination was done by TRC-50IX Fundus Camera and Topcon IMAGEnet

2000 (Topcon Co. Ltd., Japan) program. In this study, 134 eyes of 107 patients were included. Gender, age, DM duration, presence of systemic hypertension were obtained from file data. HbA_{1C} values were recorded before IVTA to evaluate glycemic control. In eyes that underwent cataract surgery after IVTA, the last BCVA values before cataract surgery were evaluated.

INTRAVITREAL TRIAMCINOLONE ACETONIDE (IVTA) INJECTION

Triamcinolone acetonide (Kenakort A, 40 mg/ml ampoule, Bristol-Myers Squibb Co, Princeton, NJ) was used as intravitreal corticosteroid. All patients were informed about treatment and complications. Written informed consent was obtained from each patient. IVTA injections were done under sterile conditions by the same physician. The injection was done under local anesthesia using topical 5% propacaine hydrochloride (Alcaine, Alcon Pharmaceuticals Plc, US). Irrigation of eyelashes, eyelids and periorbicular tissues was performed by antiseptic 10% povidone iodine. An eye speculum was used, and 10% povidone iodine was flushed onto conjunctiva and fornix for 30 seconds and then conjunctival irrigation was completed by saline. Triamcinolone acetonide 4 mg/0,1 mL was drawn into a tuberculin syringe and injected into vitreus on the lower quadrant 3.5 mm or 4 mm from the limbus in pseudophakic or phakic patients respectively. In order to prevent conjunctival bleeding, a slight and short pressure was applied onto injection site. Immediately after injection, intravitreal distribution of suspension and retinal perfusion were controlled by indirect ophthalmoscopy. Follow up visits were planned at first week, 1, 3 and six months, and the end of 1 and 2 year. The number of pan retinal PC and macular PC sessions before and after IVTA were recorded. The study patients was divided into three groups: IVTA group (focal or diffuse DME) (without macular PC), PC+IVTA group (focal or diffuse DME) (presence of focal or grid macular PC at least 4 months before IVTA and absence of PC after IVTA) (resistant DME), and IVTA+PC group (diffuse DME) (these patients received 1 session grid macular PC 1 month after IVTA). BCVA values were compared among the groups and also within the groups.

LASER PHOTOCOAGULATION

For topical anesthesia, 5% proparacaine hydrochloride was instilled in the eye. A stable chair was used with patient's chin rested on the slit lamp that was mounted with a laser system (Carl Zeiss Visulas 532S). Grid or focal laser was used depending on the type of the macular edema. Grid laser treatment was performed in diffuse DME, and focal laser treatment was performed in focal DME.[2] The laser settings were adjusted to 50μ spot size, and duration of 0.1 sec and power started from 50 mW and stepped up till it burned the retina with light gray burn. Laser burns were at least 500 μm away from the centre of the fovea. The number of laser burn given was based on the severity of DME.

STATISTICAL ANALYSIS

A statistics package program was used (Statistica Axa 7.1, Serial number: AXA507C775506 FAN3). Normal distribution of variates were tested by single sample Kolmogorov-Smirnov test. For parametric variables independent samples t-test, and for non-parametric variables Mann-Whitney U test were used. Intergroup comparisons were done by paired t-test and Wilcoxon matched pairs signed ranks test. A p value lower than 0.05 was accepted as statistically significant.

RESULTS

The study included 134 eyes of 107 patients (M/F, 52/55; Mean age±SD, 66.4±9.1 years, range 45-88). Duration of diabetes ranged between 1 year and 40 years (mean±SD 16.4±7.8 yr). The mean (±SD) HbA_{1c} value was 8.6 (±1.9, range 5.1-15.0 mg/dL). Fifty-seven patients had systemic hypertension. The mean follow-up period after IVTA injection was 15.8±16.2 months (range, 1-65 month). The baseline values of the patients were given in Table 1. The three study groups were similar in terms of mean age and gender distribution (Table 1). HbA_{1c} levels were also similar among the groups. Com-

TABLE 1: Baseline values of 134 eyes before IVTA in 107 patients

	PC+IVTA group	IVTA group	IVTA+PC at 1. month
Eye, n	46	37	51
Male/Female	12/21	18/16	22/18
Age, year	68.85±8.6	67.38±.7	63.1±9.0
DM duration, year	20.8±7.5	17.2±6.9	12.2±6.6
HbA1C	8.7±2.1	8.3±2.0	8.7±1.8
Systemic HT, n	24/33	16/34	17/40
IOP, mmHg	13.6±2.6	13.2±2.9	14.5±2.1
Previous PRPC	21/46	5/37	8/51
Previous macular PC	46/46	0/37	0/51

IVTA: Intravitreal triamcinolone acetonide; PC: Photocoagulation; DM: Diabetes mellitus; HT: Hypertension; IOP: Intraocular pressure; PRPC: Panretinal photocoagulation.

parisons of BCVA values among the groups were given (Table 2). Comparisons of BCVA values at all time points resulted that the differences were statistically non-significant. We also performed intergroup comparisons through the two years follow-up period. VA significantly increased at 1.week, 1. month, 3. month and 6. month when compared to pre-injection value (p=0.01, p=0.001, p=0.006 and p=0.01, respectively). Comparative changes of BCVA (LogMAR) in the three study groups throughout the study period were showed (Figure 1). All study groups showed significant improvement in BCVA in the first six months. At the end of 2 years follow-up period, the number of eyes that underwent cataract surgery was 2 (5%) in IVTA group, 6 (13%) in the PC+IVTA group, and 3 (6%) in the IVTA+PC group. The earliest cataract surgery was performed ten months after the injection. None of the patients showed endophthalmitis or retinal detachment. The number of patients who showed at least one IOP measurement above 20 mmHg was 8 in IVTA group, 7 in PC+IVTA group and 10 in IVTA+PC group. In five (4%) patients, secondary glaucoma was diagnosed (2 in IVTA, 2 in PC+IVTA, 1 in IVTA+PC). These IOP increases controlled by one medication and none of the patients required trabeculectomy.

DISCUSSION

The main finding of this study is that intravitreal triamcinolone acetonide injection combined with photocoagulation or alone resulted in similar improvement in visual acuity in patients with DME. DME is one of the most common reasons for vision loss in patients with DR. Focal macular PC is used for treatment of focal DME, but macular PC is not very effective in diffuse DME. Recently, intravitreal injection of triamcinolone acetonide resulted in beneficial effects in the treatment of diffuse DME that was unresponsive to laser (resistant DME). Although IVTA is known to be effective in DME, there are inconsistent results on the duration and amount of improvement in VA.

Massin et al. studied resistant DME patients after macular PC and they applied IVTA to one eye of 12 patients whereas contralateral eyes were used as the control eyes.[9] VA levels of IVTA eyes were similar with the control eyes at 1, 3, and 6. months. Dehghan et al. applied IVTA to 45 eyes and placebo to 43 eyes.[10] VA levels were better in the 2nd and

TABLE 2: Comparison of best corrected visual acuity (BCVA, LogMAR) in study groups.

	PC + IVTA	p	IVTA	p	IVTA+PC
Baseline	0.82±0.6 (n=46)	0.6	0.69±0.4 (n=37)	0.6	0.74±0.5 (n=51)
1.week	0.74±0.6 (n=38)	0.7	0.66±0.5 (n=33)	0.8	0.62±0.5 (n=13)
1.month	0.65±0.5 (n=41)	0.2	0.50±0.3 (n=29)	0.7	0.53±0.3 (n=50)
3.month	0.68±0.5 (n=31)	0.1	0.46±0.3 (n=21)	0.4	0.56±0.4 (n=28)
6.month	0.66±0.5 (n=35)	0.2	0.43±0.2 (n=16)	0.5	0.52±0.4 (n=31)
1.year	0.77±0.7 (n=33)	0.4	0.52±0.3 (n=15)	0.3	0.73±0.5 (n=16)
2.year	0.71±0.5 (n=21)	0.1	1.15±0.7 (n=8)	0.07	0.62±0.6 (n=9)

IVTA: Intravitreal triamcinolone acetonide; PC: Photocoagulation; BCVA: Best-corrected visual acuity; LogMAR: Logarithm of minimum angle of resolution. p values: Mann-Whitney U test.

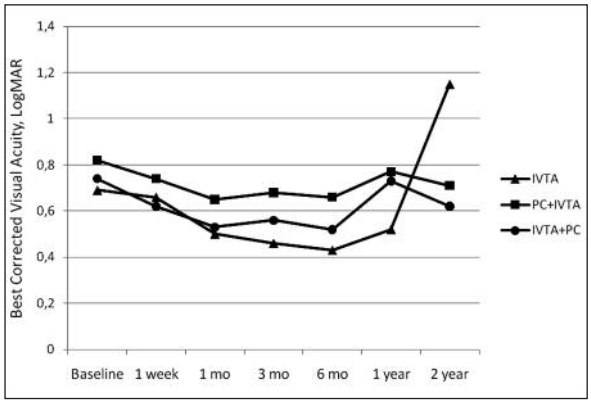

FIGURE 1: Comparison of best corrected visual acuity (BCVA, LogMAR) in study groups.
mo: Month.

4th months, but only results of 2nd month reached statistically significance level. They suggested that VA improvement was significant in patients who had PC before IVTA. Furthermore, Martidis et al. applied IVTA to eyes of 16 patients with resistant DME and they found VA increase at 1, 3, and 6. months.[11] Audren et al. studied 17 patients and they applied IVTA to one eye and used other eye as a control.[14] VA levels were significantly higher in IVTA eyes with respect to control eyes at 1, 3, and 6. months. Ciardella et al. reported significant VA increase at 6. month.[15] In our study, IVTA with or without PC provided significant improvements in VA during the first 6 months.

Lam et al. compared 10 eyes that were applied macular grid laser and IVTA with 8 eyes that were applied only IVTA.[23] While the 6 months follow-up period, the mean VA increase was higher in eyes without macular grid laser. On the other hand, Patelli et al. compared macular laser plus IVTA with only IVTA administration, and found that VA increase was similar in both groups 6 months after the injection.[24] Chieh et al., compared focal macular PC plus IVTA with only IVTA and failed to find any significant difference during 6 months.[25] In our study, macular laser PC plus IVTA group and only IVTA group resulted in similar VA at the end of 2 years. In addition, VA was worse in macular PC positive group. This result may be due to the small number of patients who attended control visits in this group. Previous studies compared PC plus IVTA with IVTA during 6 months, but no study involved a 2-year follow up period.

In recurrent macular edema, central macular thickness measured by optical coherence tomography (OCT) was similar in eyes that underwent IVTA or not.[9] The effect of IVTA is transient and DME may recur. These may limit efficacy of treatment. In the case of recurrence, repeat IVTA injection is an option; nevertheless, and IVTA combined with macular grid laser may provide longer efficacy. Kang et al., in their prospective, randomized trial of DME patients, applied IVTA to one group and IVTA plus macular grid laser to another group.[18] VA increase was similar in the first 3 months, but it was better between the 3rd and 6th months in IVTA plus macular laser group. In contrast, two previous studies reported significant VA increases during 6 months with only IVTA application.[16,17]

After IVTA, foveal thickness is reduced and retinal transparency is obtained. These effects may increase the effect of macular grid laser on photoreceptors and retinal pigment epithelium which in turn reduces recurrence of DME.[18] Lee et al., found that IVTA combined with macular grid laser achieved better results than IVTA alone in the first 6 months.[20] On the other hand, Aydın et al. failed to find any VA difference between IVTA application and IVTA plus macular laser.[19] Lam et al. found similar results.[21] We found that in both IVTA group and IVTA plus macular laser PC group, VA improved in a similar fashion. When we compared VA results of IVTA group and IVTA plus macular laser group, we found similar results in both groups.

Gillies et al. combined IVTA with macular grid PC in DME and they found no difference in the first 6 months whereas 2 years follow-up showed that patients with VA increase were 2 times higher in IVTA plus PC group than in only IVTA group.[26,27] In our study, VA results of IVTA group and IVTA plus PC group were similar. We suggest that IVTA and then macular laser PC in the first month after injection may reduce VA loss at the end of 2 years. Previous studies included a smaller number of patients with a shorter follow-up period.

The incidence and progression of DME are correlated with the duration of diabetes, metabolic control of diabetes, presence of hyperlipidemia and presence of hypertension.[28-31] In our study, these factors can lead to recurrence of macular edema and reduce efficacy of IVTA or macular PC treatment.

Intravitreal injection may lead to some complications such as endophthalmitis, cataract, and intraocular pressure increase. Therefore, IVTA has lost its popularity due to these complications. In our study, the number of patients with an IOP value higher than 20 mmHg was high. But, this was temporary and the rate of persistent secondary glaucoma was 4% at the end of 2 years in our study. These cases were controlled by medication.

There are several limitations of this study. Lack of only macular laser PC group limits our comparisons. Although our follow-up period was 2 years, the number of patients who completed the whole follow-up period was small. Within the group comparisons enabled some compensation. The rate of VA increase is quite low in patients who received only PC treatment. Therefore, a 6-month VA increase after IVTA is important for patients with DME. Increase in macular edema reverses VA improvement, but this period increases patient satisfaction. In an addition absence of OCT findings, limits our comparisons. We could only investigate functional improvement. The absence of OCT findings has led to not investigate anatomical improvement.

In conclusion, with or without macular PC, IVTA should be considered in DME treatment due to its VA improving effect for 6 months. IVTA reduces macular edema by decreasing VEGF production, anti-inflammatory effects and improving tight junctions of endothelial cells and stabilizing inner blood-retina barrier.[6-8] For this reason, we thought that IVTA led to improvement on VA values in all three groups.

Furthermore, macular PC after IVTA may postpone recurrence of macular edema in the late period.

REFERENCES

1. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. Ophthalmology 1984;91(12): 1464-74.
2. 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.
3. McDonald HR, Schatz H. Grid photocoagulation for diffuse macular edema. Retina 1985; 5(2):65-72.
4. Olk RJ. Modified grid argon (blue-green) laser photocoagulation for diffuse diabetic macular edema. Ophthalmology 1986;93(7):938-50.
5. Machemer R, Sugita G, Tano Y. Treatment of intraocular proliferations with intravitreal steroids. Trans Am Ophthalmol Soc 1979;77: 171-80.
6. Edelman JL, Lutz D, Castro MR. Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown. Exp Eye Res 2005;80(2):249-58.
7. Ip MS. Intravitreal injection of triamcinolone: an emerging treatment for diabetic macular edema. Diabetes Care 2004;27(7):1794-7.
8. Gardner TW, Antonetti DA, Barber AJ, LaNoue KF, Levison SW. Diabetic retinopathy: more than meets the eye. Surv Ophthalmol 2002;47(Suppl 2):S253-62.
9. Massin P, Audren F, Haouchine B, Erginay A, Bergmann JF, Benosman R, et al. Intravitreal triamcinolone acetonide for diabetic diffuse macular edema: preliminary results of a prospective controlled trial. Ophthalmology 2004;111(2):218-24; discussion 224-5.
10. Dehghan MH, Ahmadieh H, Ramezani A, Entezari M, Anisian A. A randomized, placebo-controlled clinical trial of intravitreal triamcinolone for refractory diabetic macular edema. Int Ophthalmol 2008;28(1):7-17.
11. Martidis A, Duker JS, Greenberg PB, Rogers AH, Puliafito CA, Reichel E, et al. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology 2002;109(5):920-7.
12. Negi AK, Vernon SA, Lim CS, Owen-Armstrong K. Intravitreal triamcinolone improves vision in eyes with chronic diabetic macular oedema refractory to laser photocoagulation. Eye (Lond) 2005;19(7):747-51.
13. Batioğlu F, Ozmert E, Parmak N, Celik S. Two-year results of intravitreal triamcinolone acetonide injection for the treatment of diabetic macular edema. Int Ophthalmol 2007; 27(5):299-306.
14. Audren F, Erginay A, Haouchine B, Benosman R, Conrath J, Bergmann JF, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular oedema: 6-month results of a prospective controlled trial. Acta Ophthalmol Scand 2006;84(5):624-30.
15. Ciardella AP, Klancnik J, Schiff W, Barile G, Langton K, Chang S. Intravitreal triamcinolone for the treatment of refractory diabetic macular oedema with hard exudates: an optical coherence tomography study. Br J Ophthalmol 2004;88(9):1131-6.
16. Karacorlu M, Ozdemir H, Karacorlu S, Alacali N, Mudun B, Burumcek E. Intravitreal triamcinolone as a primary therapy in diabetic macular oedema. Eye (Lond) 2005;19(4):382-6.
17. Avci R, Kaderli B, Akalp FD. Intravitreal triamcinolone injection for chronic diffuse diabetic macular oedema. Clin Experiment Ophthalmol 2006;34(1):27-32.

18. Kang SW, Sa HS, Cho HY, Kim JI. Macular grid photocoagulation after intravitreal triamcinolone acetonide for diffuse diabetic macular edema. Arch Ophthalmol 2006;124(5): 653-8.
19. Aydin E, Demir HD, Yardim H, Erkorkmaz U. Efficacy of intravitreal triamcinolone after or concomitant with laser photocoagulation in nonproliferative diabetic retinopathy with macular edema. Eur J Ophthalmol 2009;19(4): 630-7.
20. Lee HY, Lee SY, Park JS. Comparison of photocoagulation with combined intravitreal triamcinolone for diabetic macular edema. Korean J Ophthalmol 2009;23(3):153-8.
21. Lam DS, Chan CK, Mohamed S, Lai TY, Lee VY, Liu DT, et al. Intravitreal triamcinolone plus sequential grid laser versus triamcinolone or laser alone for treating diabetic macular edema: six-month outcomes. Ophthalmology 2007;114(12):2162-7.
22. Laursen ML, Moeller F, Sander B, Sjoelie AK. Subthreshold micropulse diode laser treatment in diabetic macular oedema. Br J Ophthalmol 2004;88(9):1173-9.
23. Lam DS, Chan CK, Tang EW, Li KK, Fan DS, Chan WM. Intravitreal triamcinolone for diabetic macular oedema in Chinese patients: six-month prospective longitudinal pilot study. Clin Experiment Ophthalmol 2004;32(6):569-72.
24. Patelli F, Fasolino G, Radice P, Russo S, Zumbo G, DI Tizio FM, et al. Time course of changes in retinal thickness and visual acuity after intravitreal triamcinolone acetonide for diffuse diabetic macular edema with and without previous macular laser treatment. Retina 2005;25(7):840-5.
25. Chieh JJ, Roth DB, Liu M, Belmont J, Nelson M, Regillo C, et al. Intravitreal triamcinolone acetonide for diabetic macular edema. Retina 2005;25(7):828-34.
26. Gillies MC, McAllister IL, Zhu M, Wong W, Louis D, Arnold JJ, et al. Pretreatment with intravitreal triamcinolone before laser for diabetic macular edema: 6-month results of a randomized, placebo-controlled trial. Invest Ophthalmol Vis Sci 2010;51(5):2322-8.
27. Gillies MC, McAllister IL, Zhu M, Wong W, Louis D, Arnold JJ, et al. Intravitreal triamcinolone prior to laser treatment of diabetic macular edema: 24-month results of a randomized controlled trial. Ophthalmology 2011;118(5): 866-72.
28. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329(14):977-86.
29. Lopes de Faria JM, Jalkh AE, Trempe CL, McMeel JW. Diabetic macular edema: risk factors and concomitants. Acta Ophthalmol Scand 1999;77(2):170-5.
30. Chew EY, Klein ML, Ferris FL 3rd, Remaley NA, Murphy RP, Chantry K, et al. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. Arch Ophthalmol 1996;114(9): 1079-84.
31. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS UK Prospective Diabetes Study Group. BMJ 1998; 317(7160):703-13.